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CHAPTER 5

ENVIRONMENTAL TOBACCO SMOKE AND CANCER

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Introduction

Lung cancer, an uncommon malignancy at the start of the century, has become the leading cause of cancer death in the United States (U.S. DHHS 1982). The American Cancer Society estimates that approximately 157,000 lung cancer cases will occur in the United States in 1990. Most cases are rapidly fatal and only a small proportion are cured by surgery or chemotherapy; five-year survival following diagnosis is less than 10 percent. Most lung cancers arise in the larger airways of the lung, the predominant site of deposition of inhaled particles in the size range of 0.5 to 3.0 microns in aerodynamic diameter. Primary cancer of the lung occurs in multiple histopathological patterns that are generally distinct and classifiable by conventional light microscopy. The principal types of lung cancer are squamous cell carcinoma, small cell carcinoma, adenocarcinoma, and large cell carcinoma; in the general population, these four types account for approximately 30 percent, 20 percent, 25 percent, and 15 percent, respectively, of all lung cancers (Butler et al. 1987). Bronchioloalveolar cell carcinoma represents about 5 percent of all lung cancers. The cellular origins of the various cell types have not been established, and controversy remains concerning the specificity of associations between certain cell types and specific etiologic agents. However, in nonsmokers, adenocarcinoma is the predominant type and small cell cancers occur only rarely.

The epidemic rise of lung cancer during this century stimulated laboratory and epidemiological investigation of its causes. Most of the early epidemiological evidence indicated that tobacco smoke was a potent respiratory carcinogen, and in 1964 the Advisory Committee to the Surgeon General of the U.S. Public Health Service concluded that cigarette smoking is a cause of lung cancer (U.S. PHS 1964). The numerous investigations performed subsequently have been consistent with this conclusion. The association of lung cancer with cigarette smoking is strongest for squamous cell and small cell cancers, but the other major types are also caused by cigarette smoking. In active cigarette smokers, the risk of lung cancer increases with both the amount smoked on a daily basis and

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with the duration of smoking (U.S. DHHS 1982; Doll and Peto 1978; Pathak et al. 1986). A threshold level of smoking that must be exceeded to cause lung cancer has never been demonstrated; any cigarette smoking is considered to increase lung cancer risk beyond that of the lifelong nonsmoker. In former smokers, the relative risk of lung cancer declines exponentially in comparison with those who continue to smoke.

Agents other than tobacco smoke may also cause lung cancer, and cases occur in lifelong nonsmokers. A recent study in New Mexico showed that the lifetime risks of lung cancer were 0.5 percent and 1.1 percent in female and male nonsmokers, respectively (Samet et al. 1988). Occupational exposures to arsenic, asbestos, chloromethyl ethers, chromium, coke oven fumes, nickel, and radon daughters have been linked to increased lung cancer risk, and many other occupational agents are suspect respiratory carcinogens. A family history of lung cancer is also associated with increased lung cancer risk, although a clear pattern of genetic susceptibility to lung cancer has not been demonstrated. Outdoor air pollution may contain carcinogens and indoor air may have high levels of radon, which causes cancer in exposed underground miners. Animal and human studies suggest that low consumption of vitamin A or its precursor, beta-carotene, may also increase lung cancer risk.

While studies linking active smoking to lung cancer were first published in the late 1940s and early 1950s (U.S. PHS 1964), involuntary exposure of nonsmokers to tobacco smoke was not considered as a cause of lung cancer in nonsmokers until 1981, when the first two scientific papers on this subject were published. Subsequently, many additional reports have addressed involuntary smoking as a cause of lung cancer in nonsmokers. The World Health Organization (1986), the U.S. Surgeon General (U.S. DHHS 1986), and the National Research Council (1986) have reviewed the evidence on involuntary smoking and lung cancer from human populations and judged it sufficient to support the conclusion that involuntary inhalation of tobacco smoke by nonsmokers causes cancer. This chapter reviews that evidence and the conclusions of the research organizations. The chapter also addressess the more limited evidence on involuntary smoking and cancer at sites other than the lung.

The Epidemiological Approach

Epidemiology is the scientific method used to describe the occurrence of disease in human populations and to determine the causes of disease by studying populations. Descriptive measures of disease occurrence include the incidence rate, which is the rate at which new cases of disease develop; the mortality rate, or rate of death; and the prevalence rate, which is the proportion of the population with disease. To identify the causes of disease, epidemiologists generally perform either cohort or case-control

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studies. Each type of study provides an estimate of relative risk as a measure of the association between exposure and disease. The relative risk describes the comparative occurrence of disease in exposed compared with nonexposed persons.

In a cohort study, the subjects are selected on the basis of their exposure history and followed over time for the development of disease. For example, a study of involuntary smoking and lung cancer might be performed by enrolling nonsmokers married to smokers and another group of nonsmokers married to nonsmokers. The lung cancer risk associated with marriage to a smoker would be estimated by comparing incidence of or mortality from lung cancer in the two groups.

In a case-control study, cases with the disease of interest and controls without the disease are identified and their past exposures to factors of interest are assessed, often by interview. For example, a case-control study of lung cancer and involuntary smoking might be conducted by identifying nonsmokers with lung cancer and a suitable control group, and then interviewing the subjects concerning the smoking habits of their spouses, other household members, and colleagues at work.

Each type of study has advantages and disadvantages, and the results of both types may be distorted by bias. Misclassification of exposure is of particular concern in studying lung cancer and involuntary smoking. Misclassification of exposure refers to the incorrect categorization of actually exposed subjects as nonexposed and of nonexposed as exposed. When misclassification occurs randomly, it tends to bias studies towards no association, that is showing negative results; if nonrandom, it may exaggerate or reduce the apparent effect of an exposure. With regard to involuntary smoking and lung cancer, two types of misclassification are of concern. Subjects classified as nonsmokers may have actually been active smokers and the degree of exposure of nonsmokers to the smoking of others may not be accurately classified. Misclassification of both types is discussed below in relation to specific studies.

The diagnosis of lung cancer is also subject to misclassification; a cancer that originated at another primary site and then spread to the lung may be incorrectly diagnosed as a primary cancer of the lung. For example, in the case-control study reported by Garfinkel and colleagues (Garfinkel et al. 1985), 13 percent of cases originally diagnosed as lung cancer were reclassified to other sites after histological review. With regard to exposure misclassification in this study, 40 percent of the cases initially classified as nonsmokers on the basis of information in medical charts were found to be smokers on interview. Confounding refers to bias that occurs when the effect of another risk factor is mixed with the effect of the exposure of interest; thus a confounding factor is a risk factor for disease that is associated

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with the exposure under investigation. For lung cancer in nonsmokers, potential confounding factors include indoor air pollution by radon and combustion products other than environmental tobacco smoke, ambient air pollution, and occupational exposures. Although confounding always merits consideration as an explanation for association, the diversity of the populations in which passive smoking and lung cancer have been associated argues strongly against confounding as the source of the association. Although individual studies may be affected by one or more biases, the totality of the epidemiological evidence as well as other relevant research are considered in judging whether an exposure adversely affects health. A bias potentially important in one study may be unimportant or adequately controlled in another. Thus review of all pertinent literature may show that bias cannot satisfactorily explain an association between exposure and disease.

Epidemiological Evidence on Involuntary Smoking and Lung Cancer

Evidence concerning involuntary smoking and lung cancer has been sought indirectly in descriptive data on mortality rates and directly with case-control and cohort studies. Time trends of lung cancer mortality across this century in nonsmokers have been examined with the rationale that temporally increasing exposure to environmental tobacco smoke should be paralleled by increasing mortality rates (Enstrom 1979; Garfinkel 1981). These data can only provide indirect evidence on the lung cancer risk associated with involuntary exposure to tobacco smoke. Enstrom (1979) calculated lung cancer mortality rates from various nationwide sources for the period 1914-1968 and concluded that a real increase had occurred among nonsmoking males after 1935. In contrast, Garfinkel (1981) found no time trends of lung cancer mortality in nonsmoking participants in two cohort studies, the Dorn Study of U.S. veterans, 1954-1969, and the American Cancer Society study, 1960-1972.

Most of the case-control and the cohort studies indicate increased lung cancer risk in nonsmokers married to smokers, but these studies do not uniformly show increased risk for sources of exposure other than smoking by the spouse (Tables 1 and 2). The first two major epidemiological studies were reported in 1981 by Hirayama and Trichopoulos and colleagues (Tables 1 and 2). Hirayama conducted a cohort study of 91,540 nonsmoking women in Japan. Mortality in these women was assessed over a 14-year follow-up period. The ratio of the observed to expected numbers of lung cancer deaths increased in a statistically significant pattern with the amount smoked by the husbands. The findings could not be explained by other factors, such as age and occupation of the husband, and were unchanged when the follow-up was extended by several years (Hirayama 1984). After its publication, the report of this study received intensive scrutiny, and correspondence in the British Medical Journal, which had published it, raised concern

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about various aspects of the study's methods and findings. In his responses to the correspondence, Hirayama satisfactorily answered most of the criticisms, although he could not eliminate the possibility of unreported smoking by women classified as nonsmokers. If self-reported nonsmokers married to smokers were actually more likely to be smokers, then the resulting bias would tend to indicate an increased risk from marriage to a smoker. Based on the same population, Hirayama has also reported significantly increased risk of lung cancer for nonsmoking married men whose wives smoke (Hirayama 1984).

In 1981, Trichopoulos and coworkers (1981) also reported increased lung cancer risk in nonsmoking women married to cigarette smokers (Table 2). These investigators conducted a case-control study in Athens, Greece, that included selected histological types of lung cancer and control subjects ascertained at a hospital for orthopedic disorders. The finding of increased risk was unchanged when the case and control series were enlarged (Trichopoulos et al. 1983).

The results of subsequently reported case-control studies have also demonstrated significantly increased risk of lung cancer in nonsmokers exposed to environmental tobacco smoke (Table 2). The findings from the more recent reports based on studies throughout the world greatly strengthen the evidence from the earlier studies. Several of the newer studies included relatively large numbers of nonsmokers (Garfinkel et al. 1985; Akiba et al. 1986; Dalager et al. 1986; Lam et al. 1987; Gao et al. 1987). Furthermore, in most of the newer studies, involuntary smoking was assessed in greater detail than in the earlier reports.

The results of two other investigations have also been interpreted as showing an increased lung cancer risk associated with involuntary smoking, but both of these studies have limitations. Knoth and coworkers (1983), in Germany, described 59 lung cancer cases in females of whom 39 were nonsmokers. Based on census data, these investigators projected that a much greater than expected proportion of the nonsmokers had lived in households with smokers. In another report, Gillis et al. (1984) described the preliminary results of a cohort study of 16,171 males and females in western Scotland (Table 1); exposure to tobacco smoke in the home increased the lung cancer risk for nonsmoking men but not for nonsmoking women. This observation was based on only 16 cases of lung cancer in nonsmokers, however.

Other investigations indicate lesser or no effects of exposure to environmental tobacco smoke on lung cancer risk (Tables 1 and 2). In these studies, however, the statistical uncertainty is large because of the relatively small numbers of subjects; accordingly, the apparently negative findings are statistically compatible with the findings of those studies judged as positive. Two separate case-control studies in Hong Kong, where lung cancer

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incidence rates in females are particularly high, did not indicate excess risk from involuntary smoking (Chan et al. 1979; Chan and Fung 1982; Koo et al. 1984; 1985; 1987). In the more recent of the two studies, the investigators comprehensively assessed cumulative exposure from home and workplace sources, but misclassification of exposure may have biased towards the negative results. A subsequent study in Hong Kong did find a significant association of spouse smoking and lung cancer risk (Lam et al. 1987). Lee and coworkers (Lee et al. 1986) in England reported a small case-control study with negative findings, but the statistical power of that study is limited. Another recent hospital-based case-control study, conducted in Japan, also failed to show an association between lung cancer risk and spouse smoking (Shimizu et al. 1988).

The results of the American Cancer Society's cohort study of lung cancer mortality in 176,139 nonsmoking women have also been considered by many as not showing an increased risk in those participants married to smokers (Garfinkel 1981). However, the risks for the nonsmoking women with smoking husbands were increased somewhat, but the increase was not statistically significant. Misclassification of exposure from active and involuntary smoking may have affected the results of this study. Preliminary results from a nationwide case-control study also did not demonstrate increased lung cancer risk from domestic exposure to tobacco smoke (Kabat and Wynder 1984), but the number of subjects was small. Two case-control studies of nonsmokers and smokers with selected histological types of lung cancer did not provide strong evidence for increased risk from involuntary smoking (Wu et al. 1985; Brownson et al. 1987). However, both studies included only small numbers of nonsmokers.

Conclusions on Involuntary Smoking and Lung Cancer

Scientists draw on a wide range of evidence in judging whether an agent, such as environmental tobacco smoke, causes disease. In addition to epidemiological data, the findings of laboratory studies involving in-vitro systems and of animal studies involving exposure to the agent are often relevant. Criteria have been developed for guidance in making judgments on the causality of exposure-disease relationships, but these criteria only provide guidelines, not strict rules of evidence (U.S. PHS 1964; Rothman 1986). Interpretation of the evidence on particular exposure-disease relationships often requires review by multidisciplinary panels of scientists who are instructed to reach a consensus, often in a setting of substantial uncertainty. For example, the World Health Organization regularly convenes panels of scientists to address the carcinogenicity of environmental agents.

For environmental tobacco smoke and lung cancer, the evidence has been considered by scientists convened by the International

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Agency for Research on Cancer of the World Health Organization, the National Research Council, and the U.S. Surgeon General (Table 3). All three groups concluded that environmental tobacco smoke causes lung cancer among nonsmokers, although the approach used by each group was different. Consensus among the three groups, in spite of differing methodology, strengthens the determination that involuntary smoking causes lung cancer. For all three types, the biological plausibility of this association was supported by the evidence on active smoking and lung cancer, knowledge of the constituents of environmental tobacco smoke, and data demonstrating the uptake of tobacco smoke by nonsmokers.

The International Agency for Research on Cancer of the World Health Organization (1986) reviewed the evidence available through the end of 1984. It reached its conclusion concerning involuntary smoking and lung cancer largely on the basis of biological plausibility. The agency cited the characteristics of sidestream and mainstream smoke, the absorption of tobacco smoke materials during involuntary smoking, and the nature of dose-response relationships for carcinogenesis, which project some risk for any level of exposure.

In reaching its conclusion, the National Research Council committee considered the biological plausibility of an association between environmental tobacco smoke exposure and lung cancer and the supporting epidemiological evidence, available through mid-1986. The committee carefully considered the sources of bias that may have affected the epidemiological studies and concluded that the association documented in the studies could not be attributed solely to bias. Based on a pooled analysis of the epidemiological data and adjustment for bias, the report's authors concluded that the best estimate for the excess risk of lung cancer in nonsmokers married to smokers was 25%.

The 1986 report of the U.S. Surgeon General also characterized involuntary smoking as a cause of lung cancer in nonsmokers. This conclusion was based on the extensive information already available on the carcinogenicity of active smoking, on the qualitative similarities between environmental tobacco smoke and mainstream smoke, and on the epidemiologic data on involuntary smoking.

The extent of the lung cancer hazard associated with involuntary smoking in the United States has appeared uncertain. (U.S. DHHS 1986; Weiss 1986). The epidemiological studies provide varying and imprecise measures of the risk (Tables 1 and 2), and exposures to environmental tobacco smoke have not been characterized for large and representative population samples. Thus, any risk assessments for involuntary smoking and lung cancer are subject to substantial uncertainty. Nevertheless, risk assessment can provide insight into the magnitude of the lung cancer problem posed by involuntary smoking.

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Repace and Lowrey (1985) used data on lung cancer mortality in Seventh Day Adventists, a nonsmoking group, to estimate the effect of exposure to environmental tobacco smoke in increasing lung cancer risk. Their analysis led to an estimate of 4,666 lung cancer deaths per year attributable to environmental tobacco smoke exposure. A later estimate gave 3,450 female lung cancer deaths and 1,440 male lung cancer deaths per year.(Repace and Lowrey, 1986) An appendix to the National Research Council's 1986 report provides estimates of the numbers of lung cancer deaths attributable to passive smoking. For the year 1985, the risk assessment projects approximately 1,000 lung cancer deaths in males and 2,000 to 3,000 lung cancer deaths in females attributable to environmental tobacco smoke. Wells (1988) attributed 3,000 lung cancer cases annually in the U.S. to involuntary smoking. A recent review of 9 published risk assessments of environmental tobacco smoke and lung cancer found they averaged about 4,500 ± 2,800 lung cancer deaths per year (Repace & Lowrey, 1990).

Further epidemiological studies of involuntary smoking and lung cancer are in progress. These studies should refine our understanding of exposure-response relationships for lung cancer and exposure to environmental tobacco smoke. Other investigations are addressing the characteristics and toxicity of environmental tobacco smoke and patterns of exposure to environmental tobacco smoke. While the results of these new studies will provide needed information for scientific purposes, the available data and the conclusions of the scientific community already provide a compelling rationale for reducing involuntary exposure to environmental tobacco smoke.

Involuntary Smoking and Cancer at Sites Other Than the Lung

Several reports have suggested that exposure to environmental tobacco smoke may increase risk of cancer at sites other than the lung. One study found that in children, maternal exposure to environmental tobacco smoke during pregnancy was associated with increased risk of brain tumors (Preston-Martin et al. 1982), and in another study paternal but not maternal smoking increased the risk of childhood rhabdomyosarcoma, a cancer of the soft tissues (Grufferman et al. 1982).

In adults, involuntary smoking has been linked to a generally increased risk of malignancy (Miller 1984). Several studies have examined excess risk at specific sites. Sandler and colleagues (Sandler, Everson, and Wilcox 1985a; 1985b; Sandler, Wilcox, and Everson 1985) conducted a case-control study on the effects of exposures to environmental tobacco smoke during childhood and adulthood on the risk of cancer. The cases included cancers of all types other than usual forms of skin cancer. For all sites combined, a statistically significant increase in risk was found for exposure to smoking by a parent (crude relative risk = 1.6) and

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by a spouse (crude relative risk = 1.5); the effects of these two sources of exposure were independent (Sandler, Wilcox, and Everson 1985). Statistically significant associations were also found for some individual sites. These provocative findings will require replication in additional studies. In a case-control study, such as reported by Sandler and colleagues, biased information on exposure to environmental tobacco smoke is of particular concern. In the cohort study in Japan, Hirayama (1984) found significantly increased mortality from nasal sinus cancers and from brain tumors in nonsmoking women married to smokers. In a case-control study of bladder cancer, involuntary smoking at home and at work did not increase risk (Kabat et al. 1986). Cervical cancer, which has been linked to active smoking, was associated with duration of involuntary smoking in a case-control study in Utah (Slattery et al. 1989) This unconfirmed finding needs additional investigation.

These associations of involuntary smoking with cancer at diverse sites other than the lung cannot be readily supported with arguments for biological plausibility based on evidence from active smokers. Increased risks at some of the sites, e.g., cancer of the nasal sinus and female breast cancer, have not been found in active smokers (U.S. DHHS 1982). In fact, the International Agency for Research on Cancer (WHO 1986) has concluded that effects would not be produced in involuntary smokers that would not be produced to a larger extent in active smokers.

SUMMARY

1. For exposure to environmental tobacco smoke and lung cancer, the evidence has been considered by scientists convened by the International Agency for Research on Cancer of the World Health Organization, the National Research Council, and the U.S. Surgeon General. All three groups concluded that environmental tobacco smoke causes lung cancer among nonsmokers.

2. Further research in involuntary smoking and lung cancer will refine our understanding and are scientifically necessary; however, existing scientific conclusions already provide a compelling rationale for reducing involuntary exposure to environmental tobacco smoke.

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FIGURES AND TABLES, CHAPTER 5

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TABLE 1

Cohort Studies of Involuntary Smoking and Lung Cancer

Study	Findings	Comments
91,540 nonsmoking females, 1966-1981, Japan (Hirayama 1981).	Age-occupation adjusted RR* by husbands' smoking: Nonsmokers - 1.00+ Exsmokers - 1.36 Current smokers < 20/day - 1.45 ≥ 20/day - 1.91	Trend statistically significant. All histological types of lung cancer.
176,139 nonsmoking females, 1960-1972, U.S. (Garfinkel 1981).	Age-adjusted RR by husbands' smoking: Nonsmokers - 1.00+ Current smokers < 20/day - 1.27 ≥ 20/day - 1.10	All histologies. Effect of husbands' smoking not statistically significant.
8,128 males and females, 1972-1982, Scotland (Gillis et al. 1984).	Age-adjusted RR for exposure to a tobacco smoker in the home: Males - 3.25 Females - 1.00	Preliminary, small numbers of cases.

*RR = relative risk, as estimated by the ratio of observed to expected number of lung cancer deaths.

+reference category, risk arbitrarily set to unity as the reference point for comparison.

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TABLE 2

Case-control Studies of Involuntary Smoking and Lung Cancer

Study	Findings	Comments
40 nonsmoking female cases, 149 controls, 1978-1980, Greece (Trichopoulos et al. 1981).	RR* by husband smoking: Nonsmokers - 1.0 Exsmokers - 1.8 Current smokers < 20/day - 2.4 ≥ 20/day - 3.4	Trend statistically significant. Histologies other than adenocarcinoma and bronchioloalveolar carcinoma.
84 female cases and 139 controls, 1976-1977, Hong Kong (Chan et al. 1979; Chan and Fung 1982).	RR of 0.75 associated with smoking spouse, compared to 1.0 for a nonsmoking spouse.	All histologies. Two reports are inconsistent on the exposure variable.
22 female and 8 male nonsmoking cases, 133 female and 180 male controls, U.S. (Correa et al. 1983).	RR by spouse smoking: Nonsmokers - 1.00 < 40 pack years - 1.48 ≥ 41 pack years - 3.11	Significant increase for ≥ 41 pack years. Bronchioloalveolar carcinoma excluded.
19 male and 94 female nonsmoking cases, and 110 male and 270 female nonsmoking controls, Japan (Akiba et al. 1986).	For females, RR of 1.5 if husband smoked; for males, RR of 1.8 if wife smoked.	Clinical or radiological diagnosis for 43%. All types of lung cancer.
99 nonsmoking cases and 736 controls, Louisiana, Texas, New Jersey (Dalager et al 1986).	RR for marriage to a smoking spouse was 1.5	Nearly 100% histological confirmation. All types of lung cancer.
28 nonsmoking controls, New Mexico (Humble et al. 1987).	RR for marriage to a smoking spouse was 3.2 No effect in active smokers.	All types other than bronchioloalveolar carcinoma.
77 nonsmoking cases, 2 matched control series, Sweden (Pershagen et al. 1987).	RR for marriage to a smoker was 3.3 for squamous small cell carcinomas.	No effect of exposure for other types. Study based within a cohort.

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TABLE 2 (continued)

Case-control Studies of Involuntary Smoking and Lung Cancer

Study	Findings	Comments
102 adenocarcinoma cases, 50 males and females, and 131 controls, Colorado (Brownson et al. 1987).	No effect in entire group. In nonsmoking women, RR of 1.7 for exposure ≥ 4 hrs/day, versus 1.0 for ≤3 hrs/day.	Involuntary smoking effect not significant in nonsmoking women, but only 19 such cases included.
25 male and 53 female nonsmoking cases with matched controls, 1971-1980, U.S. (Kabat and Wynder 1984).	RR not significantly increased for current exposure at home: Males - 1.26 Females - 0.92	All types. Findings negative for spouse smoking variable as well.
88 nonsmoking female cases, 1981-1982, Hong Kong (Koo et al., 1984, and 1985).	RR of 1.24 (not statistically significant) for combined home and workplace exposure versus 1.0 for nonexposed. No association with cumulative hours of exposure.	All types of lung cancer.
31 nonsmoking and 189 smoking female cases, U.S. (Wu et al. 1985).	No significant effects of exposure from parents, spouse, or workplace in smokers and nonsmokers.	Adenocarcinoma and squamous cell carcinoma only.
134 nonsmoking female cases, U.S. (Garfinkel et al. 1985).	Nonsignificant RR of 1.22 if husband smoked. Significantly increased RR of 2.11 if husband smoked 20 or more cigarettes daily at home. Significant trend of RR with number of cigarettes smoked at home by the husband.	All types of lung cancer. Careful exclusion of smokers from the case group.
15 male and 32 female nonsmoking cases, and 30 male and 66 female nonsmoking controls, England (Lee et al., 1986).	Overall RR for spouse smoking of 1.1.	Hospital-based study.

*RR = relative risk as estimated by the odds ratio.

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TABLE 3

Conclusions of the World Health Organization, National Research Council and U.S. Surgeon General on Involuntary Smoking and Lung Cancer

World Health Organization
"Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive" smoking, and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens, however, leads to the conclusion that passive smoking gives rise to some risk of cancer."
National Research Council
"The weight of evidence derived from epidemiologic studies shows an association between ETS exposure of nonsmokers and lung cancer that, taken as a whole, is unlikely to be due to chance or systematic bias. The observed estimate of increased risk is 34%, largely for spouses of smokers compared with spouses of nonsmokers."
U.S. Surgeon General
"Involuntary smoking can cause lung cancer in nonsmokers." "The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS leads to the conclusion that involuntary smoking is a cause of lung cancer."

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CHAPTER 6

PASSIVE SMOKING AND HEART DISEASE: EPIDEMIOLOGY, PHYSIOLOGY, AND BIOCHEMISTRY[1]

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Introduction

The first disease linked to active smoking was lung cancer. It is, therefore, not surprising that the first disease linked to passive smoking was also lung cancer (USPHS, 1986). Before the advent of mass marketed cigarettes, lung cancer was a rare disease. The fact that smoking is the major identifiable cause of lung cancer made identifying this link -- for both active and passive smoking -- relatively straightforward. This situation contrasts with heart disease, which has many risk factors, so it is not surprising that it took longer for the scientific community to conclude that active smoking caused heart disease (USPHS, 1983). Once the link between smoking and heart disease was established, it became clear that smoking accounted for more heart disease deaths than lung (and other) cancers because of the high prevalence of heart disease. Similarly, smoking is the most important preventable cause of coronary disease. Given this history, it is not surprising that exposure to environmental tobacco smoke (ETS) has now been linked to heart disease in nonsmokers (Wells, 1988; Kristensen, 1989) and may result in a substantial number of unnecessary coronary heart disease deaths in nonsmokers.

Most of the evidence linking ETS and coronary heart disease has appeared since the US Surgeon General (USPHS, 1986) and National Academy of Sciences (NRC, 1986) last reviewed the evidence on the health effects of ETS. Based on the information available as of early 1986, both these reports concluded that the evidence linking ETS and heart disease was equivocal and that more research was necessary before any definitive statements could be made. These conclusions were reasonable at the time they were made. In the four years since these reports were written, considerable information on both the epidemiology and biological mechanisms by which ETS may cause heart disease has accumulated from several areas of scientific investigation. In fact, most of the results

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[1]This chapter is an adaptation of a peer-reviewed manuscript of the same title (Glantz and Parmley, 1990).

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presented in this chapter were published after the 1986 Surgeon General and National Academy of Science reports.

First, there are now 11 epidemiological studies on the relationship between exposure to environmental tobacco smoke in the home and the risk of heart disease in the nonsmoking spouse of a smoker. All but one of these studies yielded a relative risk greater than 1.0. There are several lines of biologic evidence which make this association plausible. There is evidence that exposure to ETS reduces exercise tolerance of healthy individuals as well as people with existing coronary artery disease. Such reduced exercise capability is one of the landmarks of acute compromises to the coronary circulation. There is evidence, from both human and animal studies, that exposure to tobacco smoke, including passive smoking, increases aggregation of blood platelets. Such increases in platelet aggregation are an important step in the genesis of atherosclerosis. In addition, increasing platelet aggregation contributes to coronary thrombosis, the cause of acute myocardial infarction. Finally, carcinogenic agents in ETS, including benzo[a]pyrene have been shown to produce injuries to the endothelial cells which line arteries. Such injuries are the first step in the development of atherosclerosis. Thus, exposure to ETS can contribute to both short term and long term insults to the coronary circulation and the heart.

Effects of Primary Smoking

Before reviewing the evidence linking ETS with coronary artery disease, it is worth summarizing the evidence linking active smoking with coronary artery disease. This evidence was summarized in the 1983 Surgeon General's Report, which was devoted entirely to cardiovascular disease (USPHS, 1983); it concluded:

> In 1980, diseases of the circulatory system were responsible for approximately one-half of the total U.S. mortality. CHD was the single most important cause of death, accounting for approximately 30 percent of all U.S. deaths.
>
> Cigarette smoking is one of the three major independent CHD risk factors. The magnitude of the risk associated with cigarette smoking is similar to that associated with the other two major CHD risk factors, hypertension and hypercholesterolemia; however, because cigarette smoking is present in a larger percentage of the U.S. population than either hypertension or hypercholesterolemia, cigarette smoking ranks as the largest preventable cause of CHD in the United States. Cigarette smoking also acts synergistically with the other major risk factors to greatly increase the risk for CHD.
>
> Arteriosclerosis is the predominant underlying cause of cardiovascular disease, and atherosclerosis is the form of

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> arteriosclerosis that most frequently causes clinically significant disease, including CHD, atherothrombic brain infarction, atherosclerotic aortic disease, and atherosclerotic peripheral vascular disease. Cigarette smoking contributes both to the development of atherosclerotic lesions and to the clinical manifestations of atherosclerotic vascular disease, including sudden death. Although the precise pathophysiologic basis of these clinical manifestations is not understood, it may be related to several deleterious cardiovascular effects of cigarette smoking, including production of an imbalance between myocardial oxygen supply and demand, a decrease in threshold for ventricular fibrillation, and an increase in platelet aggregation. Nicotine and carbon monoxide are the tobacco smoke constituents most closely associated with these adverse effects; other cigarette smoke constituents such as hydrogen cyanide, oxides of nitrogen, and carbon disulfide are being studied for possible pathologic cardiovascular effects.

Since 1983, evidence has also mounted that the polycyclic aromatic hydrocarbons in cigarette smoke can injure the arterial endothelium and initiate the atherosclerotic process.

All the compounds implicated as damaging to the cardiovascular system of smokers have been identified in ETS (USPHS, 1986; NRC, 1986).

Epidemiological Studies on ETS and Heart Disease

Since 1984, the epidemiological evidence linking exposure to ETS with heart disease has rapidly accumulated. The results of the eleven published studies are summarized in Table 1 and Figure 1; four studies present data on men, nine on women, and one on both sexes combined. Despite minor differences in methodology or end points (some used death from ischemic heart disease of any origin and some were limited to death from myocardial infarction), the results of these studies are remarkably consistent. All the studies on men yielded relative risks of death from heart disease exceeding 1 for nonsmoking men married to smokers, with a median risk of 1.2. All but one of the studies on women (Lee et al, 1986) yielded relative risks exceeding 1, with a median relative risk of 1.4. Several studies also suggested an increase in the risk of nonfatal coronary symptoms (Svendsen et al, 1987; Palmer et al, 1988; Hole et al, 1989; Dobson et al, 1990); quantitative results in Table 1 only reflect risk of death, not coronary symptoms. Consistency of an observation across different studies increases the confidence one can have in the belief that an association is causal, unless all studies have the same bias.

When interpreting the results of such epidemiological studies, it is always important to consider biological plausibility and potential confounding variables which could explain the results.

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Aside from noting that the compounds in mainstream smoke that have been implicated in heart disease are in ETS, we will defer the discussion of biological plausibility until later in this chapter, when we discuss the effects of ETS on platelets and the atherogenic agents in ETS. For now, we will concentrate on potential confounding variables. These are particularly important in a disease like heart disease, because it is known to be caused by multiple risk factors.

All of the studies controlled for the most important confounding variable, age, and several (Garland et al, 1985; Svedsen et al, 1987; He, 1989; Hole et al, 1989; Humble et al, 1990) controlled for several known risk factors for coronary artery disease, in particular levels of cholesterol, blood pressure and weight (or body mass or body mass index). Most of the studies also included one or more measures of socioeconomic status, such as the nature of the housing or amount of education.

Lee (1988, 1989, 1990) has suggested that the elevated risk of heart (and other) disease with passive smoking could be due to misclassification of nonsmokers who are really smokers. In addition, Wald (1986) has noted that some people who say they live with nonsmokers have detectable levels of the nicotine metabolite cotinine in their blood, indicating that they are actually exposed to ETS, either at work or at home. The former type of misclassification will tend to lead to an overestimate of the risks associated with ETS and the latter will lead to an underestimate of the risk. Careful analysis of the question of misclassification -- which applies generally to studies of ETS and not just heart disease -- have demonstrated that the observed risks cannot be explained by this technical problem (Wald, 1986; Wells, 1986, 1988, 1990; Kawachi and Pearce, 1989; Reinken, 1989). In addition, both the Surgeon General (USPHS, 1986) and the National Academy of Sciences (NRC, 1986) were presented with the argument that misclassification errors accounted for the link between ETS and lung cancer and concluded that ETS caused lung cancer in healthy nonsmokers. To date, no compelling case has been made that this technical error explains consistent findings linking ETS with heart (or lung) disease. Indeed, the net effect of these two types of misclassification errors is to lead to an underestimate of the effects of passive smoking for lung cancer.

There is always the possibility that there is some other confounding variable relating to cultural factors, such as the nature of housing or employment or the nature of time spent outside the home. Most studies look only at a crude measure of exposure—spouse smoking—and it is possible that this is an indicator variable for other things, such as poor diet, risky lifestyle, or stress. The fact that results are similar from all over the world in widely varying cultural settings -- including several regions in the United States, the United Kingdom, Japan, and China -- argues against this concern.

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Several authors also observed a dose-response relationship (Table 1) between increasing amounts of smoking by the spouse and the risk of heart disease in the nonsmoking spouse (Helsing et al, 1988 (statistically significant in women, but not men); Hole et al, 1989; Garland et al, 1985 (although not statistically significant); Humble et al, 1990; He, 1989; Hirayama, 1984). The presence of such dose-response effects across multiple studies, done in different locations with different criteria supports the hypothesis that the epidemiology is revealing a real effect of ETS on heart disease in nonsmokers.

While all but one of the studies in Table 1 and Figure 1 yielded relative risks greater than 1, the fact remains that 3 of the studies in men and 4 of the studies in women had 95% confidence intervals for the relative risk of passive smoking for heart disease that fell below 1.0, meaning that the risk was not statistically significantly elevated above 1.0 (with $P<.05$). It is important to note that the 95% confidence intervals do not lie symmetrically about 1.0, but rather are skewed towards higher risks. To avoid false negative conclusions, Rothman (1978) suggested examining the confidence interval, as we have done, in concluding the exposure to ETS elevates the risk of heart disease.

One can assess formally how confident one can be in reaching a negative conclusion by computing the power of the study to detect an effect of specified size (Friedman et al, 1978). Table 1 shows estimates of the power of each of the studies to detect a 20% increase in risk of heart disease (i.e., a relative risk of 1.2) with the available samples. The power was computed as described in Muhm and Olshan (1989), using a two-sided test for the relative risk with a Type I risk of 5% (i.e., requiring the 95% confidence interval for the relative risk to exclude 1.0 before concluding a statistically significant elevation in risk in an individual study). Most of the studies have low to moderate power. The two (Helsing et al, 1988; Hole et al, 1989) that have power above the desirable level of 80% both identified significant increases of heart disease risk with ETS exposure. Interestingly, the study by Lee (1986) which was the only one with a relative risk below 1, also had the lowest power to detect an effect, only 3%.

It is possible to combine the results of these studies in a formal analysis to derive a global estimate of the relative risk and associated 95% confidence interval. By combining the studies, the sample size and so the power to detect an effect increases. Pooling the studies in Table 1 yields an estimate of the relative risk of death from heart disease of 1.3 (95% CI 1.1-1.6) for men and 1.3 (95% CI 1.2-1.4) for women. These results are consistent with those reported by Wells (1988) who used the studies by Gillis et al (1984), Lee et al (1986), and Helsing et al (1987) to compute a pooled relative risk of 1.3 (with a 95% confidence interval from 1.1 to 1.6) for men and the studies by Hirayama (1984), Gillis et

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al (1984), Garland et al (1985), Helsing et al (1988), Lee et al (1986), and Martin et al (1986) to compute a pooled relative risk of 1.2 (with a 95% confidence interval from 1.1 to 1.4) for women. Exposure to ETS significantly ($p < 0.001$) increases the risk of death from heart disease in nonsmokers.

Finally, it is worth noting that all these studies are based on the smoking habits of the nonsmoker's spouse, and so exposure to ETS at home. Household exposures to ETS at home are generally much smaller than exposures at work, where the density of smokers is generally higher (Repace and Lowrey, 1985,1987). As a result, these studies will generally underestimate the risk and attendant public health burden due to ETS-induced heart disease if a substantial proportion of the controls are exposed at work. Kawachi et al (1989) have adjusted Wells' (1988) relative risks to account for workplace exposures to ETS and found that the relative risks increase to 2.3 (95% CI 1.4 - 3.4) for men and 1.9 (95% CI 1.4 - 2.5) for women. In addition, Wells (1988) and Kawachi et al (1989) indicate that the number of heart disease deaths due to passive smoking is an order of magnitude greater than the number of lung cancer deaths due to passive smoking.

These epidemiological studies demonstrate a connection between ETS exposure and death from heart disease. We now turn our attention to possible physiological and biochemical mechanisms which could explain these observations.

Acute Effects of ETS Exposure

Chronic exposure to ETS exerts carcinogenic effects by increasing the cumulative risk of a molecule of one of the carcinogens in the ETS damaging the DNA in a cell and initiating or promoting the carcinogenic process. To date, no one has identified any effects of acute exposure to ETS (or, for that matter, any other carcinogen) on cancer. The situation with heart disease is different. In heart disease there are both important chronic changes (i.e., the development of atherosclerotic lesions) and acute changes. The latter include an increase in myocardial oxygen demand which may outstrip the oxygen supply and produce ischemia, and increased platelet aggregation which can lead to coronary thrombosis and acute myocardial infarction.

When the coronary circulation cannot provide enough oxygen to the myocardium to meet the demand, the result is ischemia which can be silent or result in anginal chest pain. Earlier onset of angina or hypotension during exercise is a reflection of more severe heart disease. Oxygen supply can be reduced by atherosclerotic narrowing or vasoconstriction of the coronaries or by reducing the oxygen carrying capacity of the blood by forming carboxyhemoglobin. Khalfen and Klochkov (1987) confirmed earlier work by Aronow (1978) demonstrating that exposure to ETS significantly reduced exercise ability in patients with coronary artery disease and the rate

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pressure product (heart rate times systolic blood pressure). In both studies, patients were exposed to realistic levels of ETS by simply sitting in a waiting room while someone was smoking. These effects were present in both smokers and nonsmokers (Khalfen and Klochkov, 1987) and regardless of whether or not the room was ventilated (Aronow, 1978; Khalfen and Klochkov, 1987). Exposure to ETS also increased resting heart rate and systolic and diastolic blood pressure, and resulted in a lower heart rate at the onset of angina (Aronow, 1978). Blood carboxyhemoglobin was increased by about 1% after exposure to ETS (Aronow, 1978). Sheps et al (1987) found no change in cardiovascular function in subjects with angina in response to mild elevation in blood carbon monoxide similar to that experienced in passive smokers when they exposed their subjects to pure carbon monoxide. In contrast, Allred et al (1989) found a significant dose-response relation between carboxyhemoglobin level and the change in the length of time to both electrocardiographic and symptom manifestation in men with angina pectoris exercising after exposure to CO. Even a small increase in the carboxyhemoglobin level, representing a seemingly minor reduction in the oxygen-carrying capacity of hemoglobin, was associated with the statistically significant effects. Acute exposure to ETS leads to an imbalance between myocardial oxygen supply and demand during exercise in patients with coronary artery disease. While this discussion has concentrated on the carbon monoxide in ETS as the active agent, it is likely that some other component of the ETS is also contributing to this effect.

The effects of ETS on cardiac performance are, in fact, severe enough to affect exercise performance in young healthy subjects with no evidence of heart disease. McMurray et al (1985) blindly exposed young healthy women to pure air and air contaminated with ETS while they exercised on a treadmill. The results were similar to those observed in patients with coronary artery disease. Resting heart rate was increased during exposure to ETS, which increased blood carboxyhemoglobin by about 1%. Exposure to ETS significantly reduced maximum oxygen uptake (by 0.25l/min and time to exhaustion (by 2.1 min). Exposure to ETS also increased the perceived level of exertion during exercise, maximum heart rate, and CO_2 output. It also significantly increased levels of lactate in venous blood (from a mean of 5.5 mM during control period to 6.8 mM after exposure to ETS). This greater lactate at a lower oxygen consumption during the passive smoking trials indicates a greater reliance on anaerobic metabolism. The combined effect of the reduced oxygen carrying capacity and increased lactate resulted in a reduction in maximal aerobic power and the duration of exercise. Thus, even in healthy subjects, exposure to ETS adversely affects exercise performance.

The acute effects of CO and direct tobacco smoke on exercise performance are well documented in the literature. Exposure to CO (or CO in tobacco smoke), and the subsequent elevation of blood carboxyhemoglobin levels to ca. 3%, has been shown to decrease

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exercise duration in patients with ischemic heart disease and decrease short-term maximal exercise duration in young healthy men. It is conceivable, therefore, that elevations in COHb due to ETS could have similar effects. While the association between active smoking and cardiovascular disease is well known (USPHS, 1983), little is known about the relative importance of each component of tobacco smoke that may be responsible for this relationship. Most experts agree, however, that both CO and nicotine are important, and other constituents of the smoke may play a role as well. Active smoking clearly aggravates the decrease in O_2 capacity induced by CO through an increase in the O_2 demand of the heart (Deanfield et al, 1986). Passive smoking exposes an individual to all components in the cigarette smoke, but the CO component dominates heavily because only 1% or less of the nicotine is absorbed from passive smoking compared to 100% in an active smoker (Wall et al, 1988; Jarvis, 1987). Currently available information indicates that acute exposure (1 to 2 h) to passive smoke will increase a nonsmoker's COHb level by about 1% (Jarvis, 1987). This small incremental increase in COHb due to ETS alone may not be enough to trigger acute cardiovascular effects unless combined with other sources of CO or with other components of ETS having a similar effect (e.g., nicotine).

Lamb (1984) has suggested that at maximal exertion levels, up to 90% of the oxygen carrying capacity of the blood may be needed. Because of the carbon monoxide, and perhaps other constituents, ETS reduces this capacity, so the muscle cannot maintain its high rate of aerobic metabolism unless cardiac output is further increased; people with heart disease and reduced ventricular reserve have difficulty meeting this demand. In sum, exposure to ETS increases the demands on the heart during exercise and reduces the capacity of the heart to respond. This imbalance increases the ischemic stress of exercise in patients with existing coronary artery disease and can acutely precipitate symptoms.

Moskowitz et al (1990) found evidence that adolescent children of parents who smoked may suffer from chronic tissue hypoxia such as that observed in anemia, chronic pulmonary disease, cyanotic heart disease or high altitude. These children had significantly elevated levels of 2,3-diphosphoglycerate (DPG), which suggests that the body is attempting to compensate for hypoxia by increasing DPG level in blood to meet tissue oxygen requirements, even after correcting for age, weight, height and sex. These changes were dose-dependent; the greater the exposure to ETS (measured both in terms of parental smoking and serum thiocyanate in the children), the greater the increase in DPG.

There is also evidence that acute exposure to ETS directly affects the myocardial muscle at a cellular level. Gvozdjáková et al (1984) exposed rabbits in a 50 liter child's incubator to the smoke of three burning cigarettes smoked over a 30 minute period and measured several variables related to the metabolism of cardiac

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mitochondria. (Mitochondria are the subcellular elements that control cellular respiration; they convert oxygen into usable energy in the form of ATP.) They had three groups of rabbits: one group exposed to a single dose of ETS, one group exposed to 30 min of ETS twice daily for two weeks, and one group exposed to 30 minutes of ETS twice a day for eight weeks. They measured mitochondrial respiration (QO_2) as the consumption of oxygen after adding ADP to a vessel containing mitochondrial fragments. Using pyruvate as a substrate, mitochondrial respiration QO_2 was reduced significantly compared to control (pure air) for all doses of ETS, even a single exposure (Figure 2), to about half the control value. The oxidative phosphorylation rate was also reduced significantly at all exposures by about one-third. There were no significant changes in the coefficient of oxidative phosphorylation ($ADP:O_2$) with ETS exposure. Gvozdjáková et al concluded that pyruvate as a substrate was a sensitive indicator of the toxic action of the ETS on the oxidative process.

Later, to further isolate where in the process of mitochondrial respiration, the ETS acted, Gvozdják et al (1985, 1987) reported data on succinate, NADH, and cytochrome oxidase activity in the mitochondria in the four groups of rabbits. Figure 2 shows the results of exposure to ETS on the activity of NADH oxidase, succinate oxidase and cytochrome oxidase of myocardial mitochondria. The activity of the first two oxidases exhibited no changes compared with the control group -- neither after a single exposure to ETS or following exposures up to 2 weeks. Cytochrome oxidase activity decreased both after a single exposure to ETS and over time, with increasing effects as the duration of exposure to ETS is extended. The observation that cytochrome oxidase and not NADH or succinate oxidase activity was affected by ETS suggests that the deleterious effects of ETS on myocardial mitochondrial respiration occur at the terminal segment of the mitochondrial respiration process.

Prolonged exposure to carbon monoxide has been shown in some studies to induce ultrastructural changes in myocardium (Kjeldsen et al, 1974; Thomsen and Kjeldsen, 1974; Lough, 1978). Later, Kjeldsen and co-workers (Hugod et al, 1978), using a blind technique and the same criteria to assess morphological myocardial damage found no significant changes in the coronary arteries or aorta in normocholesterolemic rabbits exposed to CO at concentrations from 200 to 4000 ppm for up to 12 weeks. They suggested that the positive results obtained earlier were due to the non-blind evaluation techniques and the small number of animals used in these studies. Later, Hugod (1981) confirmed these negative results using electron microscopy. In addition, the earlier studies were conducted at "moderate" levels of CO (100 to 150 ppm) which are considerably higher than levels of CO found in smoke-polluted environments (reported to be as high as 40-50 ppm, but more typically are around 10 ppm) (NRC, 1986). These negative studies only argue against an effect of CO in inducing coronary

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atherosclerosis, and not a direct effect of CO on myocardial oxygen supply and demand (Deanfield et al, 1986).

Acute exposure to ETS not only increases the demand and compromises the supply of oxygen to the heart as a whole, but also reduces the myocardium's ability to use this oxygen to create ATP to provide energy to support the heart's pumping activity. This effect probably results from several of the compounds in ETS acting simultaneously on the cardiovascular system.

Effects on Platelets

The action of ETS to increase platelet aggregation is another way in which ETS can acutely increase the risk of a coronary event. When blood platelets aggregate inappropriately and form a thrombus (blood clot), this clot can form in a fissured plaque in the coronary circulation and precipitate a myocardial infarction. Platelets are important for the normal body process of hemostasis, to prevent blood loss after an injury. Hemostasis depends on complex interactions among the dynamics of blood flow, components of the vessel wall, blood platelets and plasma proteins. A thrombus can be considered as an inappropriate form of hemostasis and is composed of a mass of cellular material held together by a network of fribrin. Definitive evidence has confirmed that platelets play a major role in thrombus formation and embolization, especially in the arterial system. In addition, increasing evidence has shown that platelet deposition and thrombus formation can contribute to the growth and progression of atherosclerotic plaques (Fuster and Chesebro, 1981; Ross, 1986). An arterial thrombus appears to develop in three phases: platelet adhesion, platelet aggregation, and activating of clotting mechanisms. Passive smoking increases platelet aggregation and so increases the likelihood of thrombus formation and myocardial infarction.

Table 2 summarizes the results of three studies (Davis et al, 1985a, 1986, 1989) on the effects of cigarette smoke on platelet aggregation and damage to the arterial endothelium (lining). (We will discuss the effects on the endothelium below.) Davis et al (1989) also measured platelet aggregate ratios and endothelial cell counts in nonsmokers before and after being exposed to 20 minutes of ETS while sitting in a hospital atrium. Mean values before and after passive smoking were 0.87 and 0.78 (P=.002) for platelet aggregate ratios and 2.8 and 3.7 (P=.002) for counts of anuclear endothelial cell carcasses in venous blood. These changes are in between the effects observed after nonsmokers smoked two tobacco cigarettes and the effects observed after smoking two non-tobacco cigarettes (Davis et al, 1985a) and similar to the values observed in nonsmokers who smoked two cigarettes while trying not to inhale (Davis et al, 1986). These effects were not correlated with the level of nicotine in the blood of the experimental subjects in any of these or other (Davis et al, 1985, 1987), related studies on how drugs modify platelet aggregation and endothelial cell counts. In

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particular, the effects observed in nonsmokers smoking without inhaling were similar to the effects on smokers smoking two cigarettes, despite the fact that the plasma nicotine levels in the nonsmokers were a factor of 5 smaller than those observed in the smokers (Davis et al, 1986). Other work in the same laboratory comparing smoking with snuff use revealed similar changes in platelet function in response to these two forms of tobacco use (Davis et al, 1990). This result, combined with the finding that smoking non-tobacco cigarettes (Davis et al, 1985a) failed to produce changes in platelet function as large as observed with tobacco cigarettes, suggests that nicotine is an important active agent. Since non-tobacco cigarettes also affected platelet aggregation somewhat, however, it is possible that carbon monoxide or other combustion products are also influencing the platelets.

Sinzinger and Kefalides (1982) measured platelet sensitivity to antiaggregatory prostaglandins (E_1, I_2, and D_2) before, during and after 15 minutes of exposure to ETS in healthy nonsmokers and smokers (Table 3). Passive smoking reduced platelet sensitivity to the antiaggregatory prostaglandins I_2 and E_2 significantly ($P<.01$) by a factor of about 2 by the end of 15 minutes exposure to ETS among nonsmokers. This effect persisted at 20 minutes after the end of exposure, and was gone by 40 minutes. Platelet response to prostaglandin D_2 changed modestly in a similar pattern, but did not reach statistical significance. Among smokers, the control level of platelet aggregation was higher ($P<.01$) and the prostaglandins had no significant effects on platelet aggregation over time during or following exposure to ETS. Sinzinger and Virgolini (1989) also showed that repeated exposure to ETS for one hour per day for ten days produced lasting changes in platelet function in nonsmokers similar to that observed in smokers. Thus, nonsmokers' platelets seem much more sensitive to a single exposure to ETS than do smokers' platelets, with platelet sensitivity to disaggregating prostaglandins having similar effects in nonsmokers acutely exposed to ETS as it does on the chronic levels of platelet aggregation observed in long-term smokers.

Further evidence from the same laboratory that passive smoking increases platelet aggregation comes from work by Burghuber at al (1986), who had smokers and nonsmokers smoke two cigarettes and also exposed a different group of smokers and nonsmokers to ETS in an 18 m^3 room in which 30 cigarettes had been smoked just before exposing the nonsmokers. They measured the sensitivity of platelets to the disaggregating substance prostaglandin I_2 (PGI_2), which is released by endothelium and inhibits platelet aggregation. (PGI_2 is also called prostacyclin.) Figure 3 shows the results of this experiment. In smokers, neither smoking nor passive smoking affected the sensitivity of the platelets to the disaggregating effect of prostaglandin I_2. The sensitivity of platelets in smokers was also significantly lower than nonsmokers. In contrast, platelets were more sensitive to prostaglandin I_2 in nonsmokers, with both smoking and passive smoking producing similar reduction

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in platelet sensitivity to prostaglandin I_2. These results suggest that the platelets of smokers are already desensitized to the anti-aggregatory substance prostaglandin I_2, so that no further decrease in aggregation is seen. The significant decrease in platelet sensitivity to PGI_2 after acute exposure to ETS suggests that after ETS exposure platelets are more likely to aggregate, with the adverse consequences described above.

Earlier work by Saba and Mason (1975) also indicated that nicotine increased a variety of measures of platelet aggregation in nonsmokers and smokers. While the effects of nicotine on platelets from smokers was greater than in nonsmokers, the effect generally did not vary with dose (between $2x10^{-9}$ and $2x10^{-4}$ molar), suggesting that the effects of nicotine on platelets occur at low doses and that the system saturates quickly. This observation may explain why passive and active smoking have such similar effects on platelets (Sinzinger and Kefalides, 1982; Burghuber et al, 1986; Davis et al, 1989).

The probable link between nicotine and adverse physiologic effects is nicotine-induced release of catecholamines. Catecholamines are then responsible for increased platelet aggregation. This reasoning suggests that beta blockers might provide some protection in smokers. This premise is borne out by the MAPHY trial --a trial comparing the effects of the beta blocker metoprolol to a thiazide diuretic in the control of moderate hypertension (Wilkstrand, et al, 1988). For the same reduction in blood pressure, the metoprolol treated group had a lower mortality than the thiazide treated group. Virtually all of this reduction in mortality, however, was seen in smokers, and not non-smokers. This study provides evidence that blocking the effects of catecholamines (released by nicotine) was the cause of the reduced mortality in smokers who were receiving metoprolol.

In sum, passive smoking has significant effects on platelet aggregation, of a magnitude similar to that observed in active smoking. Moreover, the response of nonsmokers to both active and passive smoking appears to be different from smokers, with nonsmokers being more sensitive to low exposures to cigarette smoke than smokers. This observation suggests that the pharmacology of ETS in nonsmokers may be different than in smokers, with nonsmokers being more sensitive to low doses of ETS. In particular, it invalidates attempts to estimate "cigarette equivalent" doses of ETS in nonsmokers or extrapolating from risks of smoking in smokers to effects of ETS on nonsmokers. The resulting increase in platelet aggregation can contribute to acute thrombus formation and myocardial infarction.

In addition to the role of platelets in acute thrombus formation, platelets are also important in the development of atherosclerosis (Ross, 1986). Once there is damage to the arterial endothelium, either through mechanical or chemical factors,

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platelets interact with or adhere to subendothelial connective tissue and initiate a sequence which leads to atherosclerotic plaque. When platelets interact with or adhere to subendocardial connective tissue, they are stimulated to release their granule contents. Endothelial cells normally prevent platelet adherence because of the nonthrombogenic character of their surface and their capacity to form antithrombotic substances such as prostacyclin. Once the endothelial cells have been damaged, the platelets can stick to them. Once the platelets are bound to the endothelium, they release mitogens such as platelet-derived growth factor (PDGF), which encourage migration and proliferation of smooth muscle cells in the region of the endothelial injury (Fox and DiCorleto, 1984). If platelet aggregation is increased because of exposure to ETS, the chances of platelets building up at an endothelial injury will also be increased. Thus, in addition to contributing to acute effects through increasing the likelihood of thrombus formation, the effects of ETS on platelets also increase the chances that endothelial injury will lead to arterial plaque.

ETS also plays a role in causing damage to the endothelium and initiating the atherosclerotic process. As discussed above, Davis et al (1989, 1986, 1985, 1987, 1985b, 1990) found that acute exposure to ETS (1989), like active smoking (1986, 1985a, 1987, 1985b) and use of chewing tobacco (1990), lead to a significant increase ($P<.002$) in the appearance of anuclear endothelial cell carcasses in the blood of people exposed to ETS (or tobacco or tobacco smoke) constituents. The appearance of these cell carcasses indicates damage to the endothelium, which is the initiating step in the atherosclerotic process. As noted above, in nonsmokers the appearance of endothelial cells following passive smoking is almost as great as following primary smoking (Table 2).

The process by which endothelial injury leads to the development of an atherosclerotic plaque, including the role of platelets, is described in Figure 4. Based on the information presented so far, exposure to ETS appears to produce injuries similar to those observed with exposure to primary smoke and also affects platelets in a way that increases the chances that they will bind to the injured area and promote growth of smooth muscle cells.

The Role of the Polycyclic Aromatic Hydrocarbons in ETS

Many atherosclerotic plaques in humans are either monoclonal or possess a predominantly monoclonal component (Benditt and Benditt, 1973), which indicates that the smooth muscle cells of each plaque have a predominant cell type. Several animal studies have also shown that injections of polycyclic aromatic hydrocarbons (PAHs), in particular 7,12-dimethylbenz(a,h)anthracene (DMBA), benzo(a)pyrene (Albert at al, 1977; Revis, et al 1984; Penn et al, 1981; Penn et al, 1986; Majesky et al, 1983) accelerate the development of atherosclerosis. Others (Rogers et al, 1980, 1988) failed to find an effect of active smoking or the extent of fatty

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deposits in the coronary arteries of baboons. (There was a significant effect on the carotid arteries.) Benzo(a)pyrene is an important element in ETS (USPHS, 1986). The effects of PAHs or other carcinogenic or mutagenic elements in ETS (Remmer, 1987) relates directly to the response to injury theory of atherogenesis discussed above (Ross, 1986). Changes in the underlying smooth muscle stimulated by these agents could then initiate the "injury" that leads to platelet aggregation and plaque formation. Thus, chronic exposure to ETS could have effects on plaque formation through mechanisms similar to that by which long term exposures produce cancer in other organs.

Albert et al (1977) gave chickens weekly intramuscular injections of DBMA and benzo(a)pyrene for up to 22 weeks, then killed the chickens at various times beginning after 13 weeks and measured the plaque volume in the chickens' aortas. They found that both DBMA and benzo(a)pyrene significantly increased the volume of plaque compared to control chickens who had just received injections of the solvent used to carry these agents. This study provided the first evidence that known carcinogenic chemicals could be atherogenic as well.

Penn et al (1981) extended this result in a similar experiment by showing that the effects of DBMA on the extent of plaque buildup in chickens was dose-dependent. The median cross-sectional area of plaques on individual aortic segments and the plaque volume index (an approximate measure of the total volume of plaque per aorta) increased in a nearly linear fashion with DBMA dose. In contrast to the marked increase in plaque area in the DBMA-treated animals, there was only a slight increase in the percentage of aortic sections with plaques in carcinogen-treated animals than in controls. Plaques with a small cross sectional area were present in all animals. Lesions of widely differing cross sectional areas appeared to be similar histologically under the light microscope. Together, these data suggest that a major effect of chronic DBMA exposure is to increase the size of spontaneous aortic lesions. Rather than inducing some sort of cancer-like change in an individual cell that begins the process which ultimately leads to formation of a plaque, Penn et al suggested that chronic DBMA exposure causes preferential division of individual cells or patches of cells within the preexisting spontaneous lesions. From this perspective, DBMA and other exogenous compounds would be acting as a mitogen, similar to that released by activated platelets, to stimulate division of aortic smooth muscle.

Revis et al (1984) found similar results in White Carneau pigeons injected with DMBA and benzo(a)pyrene weekly for 6 months, beginning when the pigeons were 3 months old. Compared with the work described above, they found a greater effect on atherogenesis of benzo(a)pyrene than DBMA, and also failed to observe a dose-response relationship between the dose given and the amount of aortic plaque. These differences from the work just described may

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FIGURES AND TABLES, CHAPTER 6

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There are eleven epidemiological studies, done in a variety of locations, which reflect a 30% increase in risk of death from ischemic heart disease or myocardial infarction among nonsmokers living with smokers. The larger studies also demonstrate a statistically significant dose-response effect, with larger exposure to ETS being associated with greater risks of death from heart disease.

These epidemiological studies are complemented by a variety of physiological and biochemical data from human studies which suggest that ETS may adversely affect platelet function and damage arterial endothelium in a way that increases the risk of heart disease. Moreover, ETS, in realistic exposures, also exerts significant effects on exercise capability of both normal people and people with heart disease by affecting the body's ability to deliver and utilize oxygen. In animal experiments, ETS also depresses cellular respiration at the level of mitochondria. The polycyclic aromatic hydrocarbons in ETS also accelerate, and may initiate, the development of atherosclerotic plaque.

It is also important to note that the cardiovascular effects of ETS appear to be different in nonsmokers and smokers. Nonsmokers appear to be more sensitive to ETS than smokers, perhaps because some of the affected systems are sensitive to low doses of the compounds in ETS, then saturate and also perhaps because of physiological adaptions smokers undergo as a result of chronic exposure to the toxins in cigarette smoke. In any event, these findings indicate that, in terms of cardiovascular disease, it is unreliable to compute "cigarette equivalents" for passive exposure to ETS, then try to extrapolate the effects of this exposure on nonsmokers from the effects of direct smoking on smokers.

These results combine to suggest that heart disease is an important consequence of exposure to ETS. The combination of epidemiological studies with demonstration of physiological changes with exposure to ETS, together with biochemical evidence that elements of ETS have significant effects on the cardiovascular system, lead to the conclusion that ETS causes heart disease. This increase in risk translates into about 10 times as many deaths from ETS-induced heart disease as lung cancer, and contributes 37,000 to the estimated 53,000 deaths annually from passive smoking (Wells, 1988). This toll makes passive smoking the third leading preventable cause of death in the United States today, behind active smoking and alcohol.

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manifestation of transformation is a relatively late event in plaque development or an early but stable event. Oncogene activation and expression is an important early event in transformation and tumor genesis. These results identify specific molecular events that may underlie the proliferation of smooth muscle cells that is a hallmark of atherosclerotic plaque development and demonstrates that plaque cells exhibit molecular alterations that had previously only been thought to be present in cancer-cell transformation and tumorigenesis. These results provide direct support for the monoclonal hypothesis.

Randerath et al (1988) also demonstrated that constituents of cigarette "tar," including benzo(a)pyrene, are preferentially attracted to the heart and damage DNA there. They studied molecular mechanisms of smoking-related carcinogenesis by examining the induction and distribution of covalent DNA damage in internal organs of the mouse following topic application of cigarette smoke condensate daily for 1, 3, or 6 days then killed 24 hr later. DNA samples were obtained from skin, lung, heart, kidney liver, and spleen. Adducts containing benzo(a)pyrene-derived moieties were identified, together with others. At all three times, the number of adducts in heart and lung DNA was about five times higher than that in liver and slightly higher than that in skin. Covalent DNA damage was estimated to be 6.2, 5.7, 3.9, and 1.9 times higher, respectively, in lung, heart, skin and kidney than in liver, ranging from approximately 1 adduct in 5.4×10^6 DNA nucleotides in lung to 1 adduct in 3.3×10^7 DNA nucleotides in liver. Spleen DNA was virtually adduct free. While the DNA adduct profiles resembled each other qualitatively among the different tissues, there were major quantitative differences between the different tissues, with the highest DNA binding occurring in the lung and heart. The reasons for the high incidence of DNA adducts in the heart are not known, but may be related to the role of plasma lipids in transporting PAHs such as benzo(a)pyrene and preferential binding of these lipids to cardiac tissue, as discussed earlier.

In sum, there is a growing body of evidence at a molecular level supporting the monoclonal hypothesis of atherogenesis, with compounds in tobacco smoke and ETS strongly implicated as agents which stimulate the development of coronary lesions. Regardless of whether the monoclonal hypothesis proves to be true (or, more likely, one of several initiators of the atherosclerotic process), the fact is that there is clear evidence that components of ETS, in particular PAHs such as benzo(a)pyrene, initiate or accelerate the development of plaque. These biochemical findings are consistent with the epidemiological finding that chimney sweeps, which are exposed to high levels of PAHs in soot, have an increased risk of heart disease (as well as cancer) and tend to develop these diseases younger than other, comparable, occupations which avoid exposure to PAHs (Hansen, 1983).

Summary

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the same birds. Thus, the PAHs seem to accelerate any preexisting tendency to develop atherosclerosis.

Regardless of the ultimate mechanism by which PAHs exhibit atherogenic effects, it seems logical to suppose that the reactive intermediary metabolites of these chemicals are the proximate atherogenic or co-atherogenic agents since the parent compounds are relatively inert both chemically and biologically. Thus, bioactivation and inactivation (and regulatory control of these processes) may be presumed to play extremely important roles in their atherogenic properties. Bioactivated chemicals vary in their stability/reactivity according to four general categories: (i) those which are extremely unstable and persist only at the immediate site (enzyme) of bioactivation, (ii) those which persist only within cells in which bioactivation occurs, (iii) those which persist primarily only within tissues in which bioactivation occurs, and (iv) those capable of being transferred in the circulation from one organ to another. For the first three of these four categories, biotransformation in the aorta per se (target tissue activation) would be of prime interest and importance. Thus, it appears that PAHs could be playing either a mutagenic or mitogenic role in beginning the atherosclerotic process in susceptible cells or individuals, depending on how the PAHs in ETS are metabolized in the aorta.

The finding that enzymes that metabolize DMBA and benzo(a)pyrene are in the artery wall led Penn et al (1986) to search for specific molecular events in plaque cells that would lead to DNA changes similar to those previously found in tumors. Identification of such processes would be supportive of the monoclonal hypothesis of atherogenesis. They obtained human DNA samples from coronary artery plaques as well as DNA from normal sections of the coronary arteries at surgery to remove the plaque. These DNA samples were tested with the NIH 3T3 cell transection assay. Foci arose in cells transfected with each of the DNA samples obtained from the human coronary plaque, with an efficiency (number of foci per μg of DNA) ranging from 0.016 to 0.060 (mean 0.036). The transfection efficiencies for DNA's from normal coronary artery, liver, spleen, lung, kidney and trachea were all below 0.008. The transformed cells were also injected into the scalps of nude mice, where they developed tumors. These results provide direct evidence for similarities on the molecular level in the development of plaques and tumors. Human coronary artery plaque DNA contains sequences capable of transforming NIH 3T3 cells and these transformed cells can cause tumors after injection into nude mice. Control experiments verified that the transforming cells did indeed contain human DNA and that the tumorigenic (or transforming) activity was not due to the ras oncogene family. Although these results clearly demonstrate that human plaque DNA has transforming ability, the temporal expression of this activity in vivo is not known. The plaques were taken from adult patients in late stages of vascular disease. Thus, we cannot determine from these samples whether the

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be related to species differences, differences in the carrier used to inject the PAHs (DMSO in the previous studies vs. corn oil in this one) or differences in the age of the pigeons or dosing schedule. They also found an increase in aortic plaques in pigeons treated with the PAH 3-methylcholanthrene, but not the carcinogen 2,4,6-trichlorophenol or the PAH benzo(e)pyrene, which is not considered a carcinogen. This result suggests that carcinogenic PAHs, rather than carcinogens or PAHs in general, are implicated in the atherosclerotic process.

Revis et al also studied the distribution of these compounds after they had been radiolabelled. Forty-eight hours after the injection of PAHs, radioactivity in the liver, aorta and lung accounted for 75% of the injected dose, whereas in animals injected with 2,4,6-trichlorophenol, radioactivity in the liver and kidney accounted for 80% of the dose. In addition, 80% of the radioactivity observed in the plasma immediately following injection of radiolabelled PAHs was associated with the LDL and HDL cholesterol fractions, compared with only 24% of the 2,3,6-trichlorophenol, suggesting that plasma lipoproteins are an important vehicle for transporting PAHs to their sites of activation in the arteries.

There is also some evidence that ETS directly affects plasma lipoproteins. Moskowitz et al (1990) showed that adolescent children whose parents smoked had elevated levels of cholesterol and depressed levels of HDL, even after correcting for age, weight, height and sex. These effects were dose dependent; the greater the exposure to ETS, the greater the changes in these variables. High cholesterol and low HDL are important for the development of plaque. Data on cholesterol and HDL from adults married to smokers, however, do not show similar differences (Garland et al, 1985; Svendsen et al, 1987).

To further elucidate the possible mechanisms by which PAHs induce atherosclerotic changes, Majesky et al (1983) gave White Carneau and Show Racer pigeons a single injection of benzo(a)pyrene, then looked for metabolites of the benzo(a)pyrene in aortic and hepatic tissues 48 hours later. White Carneau pigeons develop severe atherosclerosis by the time they are 3 years old, whereas Show Racer pigeons are relatively resistant to aortic atherosclerosis. Aortic preparations of the White Carneau strain exhibited a much greater inducibility of the microsomal monooxygenase system than did those of the Show Racer strain, particularly in young pigeons. Aortic tissues from White Carneau pigeons aged 6-12 months exhibited a 3-12 fold inducibility whereas aortic tissues from the same strain at 2-5 years of age exhibited only minor (maximum of 3.3 fold) and, for the most part, statistically insignificant increases. No age differences in inducibility could be detected in the Show Racer strain. Interestingly, the differences in inducibility manifest in aortic tissues were greater in aortic tissues than in hepatic tissues from

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TABLE 1.

Table 1
Epidemiological Studies of Environmental Tobacco Smoke and Coronary Heart Disease Death

Author	Type[a]	Location	Deaths or Cases	Relative Risk	95% Confidence Interval	Dose Response?[b]	Power[c]	Controlling for:
Males								
Gillis et al[8] (1984)	P	Scotland	32	1.3	0.7 - 2.6	-	5%	age
Lee et al[9] (1986)	C	United Kingdom	41	1.2	0.6 - 2.6	-	4%	age, marital status
Svendsen et al[10] (1987)[d]	P	United States	13	2.1	0.7 - 6.5	Yes	3%	age, blood pressure, serum cholesterol, weight, education, alcohol
Helsing et al[11] (1988)	P	Maryland	370	1.3	1.1 - 1.6	No	40%	age, marital status, housing, education
Pooled[e]				1.3	1.1 - 1.6			
Females								
Hirayama[12] (1984)	P	Japan	494	1.2	0.9 - 1.4	Yes	40%	age, diet
Gillis et al[8] (1984)	P	Scotland	21	3.6	0.9 -13.8	-	2%	age
Garland et al[13] (1985)	P	California	19	2.7	0.9 -13.6	-	2%	age, blood pressure, plasma cholesterol, weight, years of marriage
Lee et al[9] (1986)	C	United Kingdom	77	0.9	0.5 - 1.6	-	6%	age, marital status
Martin et al[14] (1986)	C	Utah	23	2.6	1.2 - 5.7	-	3%	age, family history of CHD, hypertension, diabetes, weight, alcohol, exercise
Helsing et al[11] (1988)	P	Maryland	988	1.2	1.1 - 1.4	Yes	92%	age, housing, marital status, education
He (1989)[15]	C	China	34	1.5	1.3 - 1.8	Yes	3%	age, race, residence, occupation, hypertension, family history of hypertension or CHD, alcohol, exercise, hyperlipidemia
Humble et al[16] (1990)	P	Georgia	76	1.6	1.0 - 2.6	Yes	8%	age, serum cholesterol, blood pressure, weight
Butler[18] (1990)	P	California	64	1.4	0.5 - 3.8	-	4%	age
Pooled				1.3	1.2 - 1.4			

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Table 1
Epidemiological Studies of Environmental Tobacco Smoke and Coronary Heart Disease Death

Author	Type[a]	Location	Deaths or Cases	Relative Risk	95% Confidence Interval	Dose Response?[b]	Power[c]	Controlling for:
Both sexes combined								
Hole et al[17] (1989)[f]	P	Scotland	84	2.0	1.2 - 3.4	-	10%	age, sex, social class, blood pressure, cholesterol, weight
Pooled[d]				1.3	1.2 - 1.4			

[a]P = Prospective cohort, C = Case control
[b]No entry in this column indicates no comment on the presence or absence of dose-response relationship
[c]Power to detect relative risk of 1.2 with 95% confidence
[d]High risk population; members of MRFIT trial
[e]Pooled relative risk computed as $R = \exp(\Sigma w_i \ln R_i / \Sigma w_i)$ where $w_i = (\chi_i / \ln R_i)^2$
[f]This report is a later follow-up of the population reported in Gillis et al[8]
[g]All studies combined without regard for sex, with Gillis et al[8] excluded because Hole et al[17] report later follow-up on the same people.

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Table 2
Effect of Passive and Active Smoking on Platelet Aggregation and Endothelial Cell Damage

	Platelet Aggregate Ratio			Endothelial Cell Count			n
	Before	After	Change	Before	After	Change	
Passive Smoking (nonsmoker)	.87	.78	-.09	2.8	3.7	0.9	10
Tobacco (nonsmoker) vs.	.80	.65	-.15	2.3	4.8	2.5	20
Non-tobacco cigarette (nonsmoker)	.81	.78	-.03	2.5	3.0	0.5	
Inhale cigarette (smoker) vs.	.81	.68	-.13	4.0	5.4	1.4	24
Not inhale cigarette (nonsmoker)	.82	.73	-.09	3.3	4.7	1.4	22
Smoke (smoker) vs.	.85	.70	-.15	4.4	6.4	2.0	17
Snuff (smoker)	.82	.76	-.06	3.9	4.7	0.8	

Notes: All studies are paired and reflect significant differences (P<.005). Platelet aggregate ratio is the ratio of platelet count of platelet-rich plasma, prepared immediately after venipuncture with a solution containing edetic acid and formaldehyde, to that of platelet-rich plasma prepared in the same manner, except for the absence of formaldehyde. A decrease in the platelet aggregate ratio reflects an increased formation of platelet aggregates. Endothelial cell count is mean number of anuclear cell carcasses in 0.9 μL chambers. Source: Davis et al[47,48,51,52]

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Table 3
Platelet Sensitivity to Prostaglandins Before and After Passive Smoking
(ng PG/ml platelet rich plasma)

Prostaglandin	Before	After	20 min	60 min
Nonsmokers				
I_2	1.26±0.11	2.16±0.21*	1.76±0.21*	1.35±0.19
E_2	18.7±3.1	32.5±4.2*	28.2±4.1*	24.7±2.8
D_2	42.7±3.8	55.6±5.3	51.3±4.2	44.6±4.1
Smokers				
I_2	1.75±0.26	2.08±0.16	2.06±0.15	1.93±0.23
E_2	27.8±2.3	30.6±3.5	31.0±4.1	29.1±2.9
D_2	44.9±4.1	48.6±4.8	49.8±3.7	45.2±3.8

*P<.01 compared to control. Results are mean ± SEM. Source: Sinzinger and Kefalides (1982)

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FIGURE CAPTIONS

Figure 1: Relative risk in epidemiological studies of the risk of death from coronary heart disease or myocardial infarction among nonsmokers living with smokers compared with nonsmokers living with nonsmokers. Lines indicate 95% confidence intervals. (Note that two studies have upper bounds to confidence interval off the scale of the graph.)

Figure 2: Effect of passive smoking on myocardial mitochondrial respiration. $QO_2(S_3)$ = oxygen consumption in mitochondria in the presence of the substrate and ADP; $QO_2(S_4)$ = capacity of respiratory chain without ADP added; OPR = oxidation phosphorylation rate; ADP:O = oxidation phosphorylation coefficient; RCI = respiratory control index. Source: Gvozdják et al (1987) Figures 1 and 2.

Figure 3: Effect of active (left) and passive (right) smoking on platelet aggregation in smokers and nonsmokers. The sensitivity index, SI_{PGI2}, is defined as the inverse of the concentration of prostaglandin I_2 necessary to inhibit ADP-induced platelet aggregation by 50%. Lower values of SI_{PGI2} indicate greater platelet aggregation. Source: Burghuber et al (1986) Figures 3 and 4.

Figure 4: Advanced intimal lesions of atherosclerosis may occur by at least two pathways. The pathway demonstrated by the clockwise (long) arrows to the right has been observed in experimentally induced hypercholesterolemia. Injury to the endothelium (A) may induce growth factor secretion (short arrow). Monocytes attach to endothelium (B), which may continue to secrete growth factors (short arrow). Subendothelial migration of monocytes (C) may lead to fatty-streak formation and release of growth factors such as platelet-derived growth factor (PDGF) (short arrow). Fatty streaks may become directly converted to fibrous plaques (long arrow from C to F) through release of growth factors from macrophages or endothelial cells or both. Macrophages may also stimulate or injure the overlying endothelium. In some cases, macrophages may loose lose their endothelial cover and platelet attachment may occur (D), providing three possible sources of growth factors -- platelets, macrophages, and endothelium (short arrows). Some of the smooth-muscle cells in the possible lesion itself (F) may form and secrete growth factors such as PDGF (short arrows). An alternative pathway for the development of advanced lesions of atherosclerosis is shown by the arrows from A to E to F. In this case, the endothelium may be injured but remain intact. Increased endothelial turnover may result in growth-factor formation by endothelial cells (A). This may stimulate migration of smooth-muscle as well as growth factor secretion from the "injured" endothelial cells (E). These interactions could then lead to fibrous-plaque formation and further lesion progression (F). The PAHs in ETS probably act by the second pathway. Source: Ross (1986) Figure 6.

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FIGURES AND TABLES, CHAPTER 6

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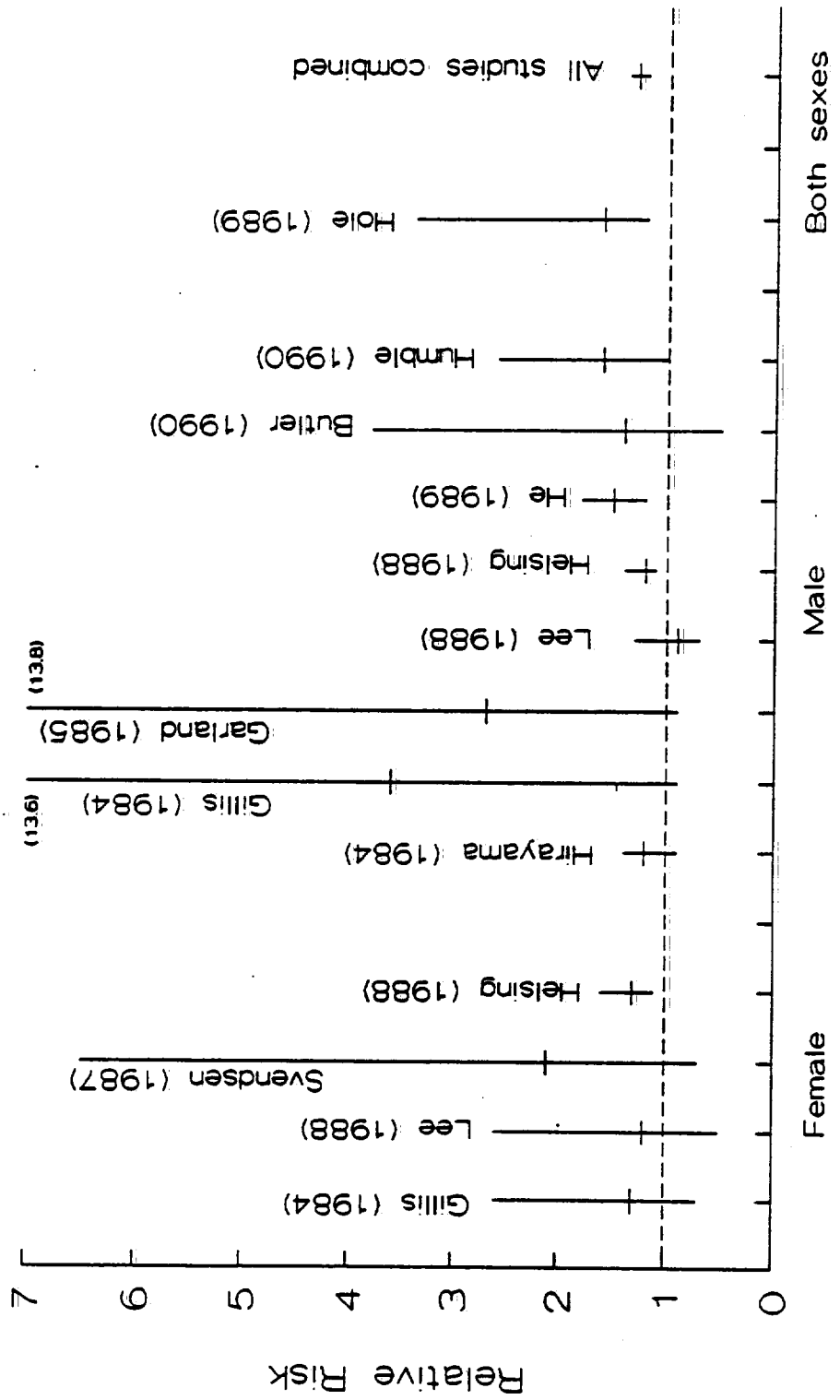

FIGURE 1.

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FIGURE 3.

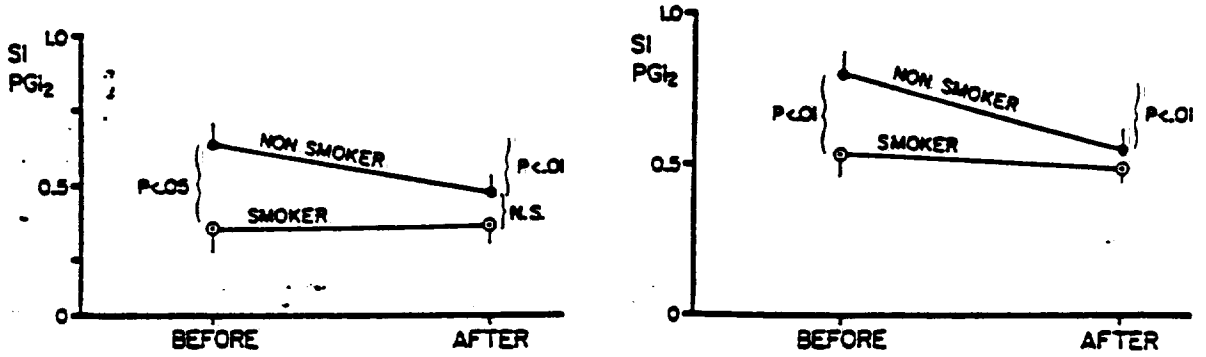

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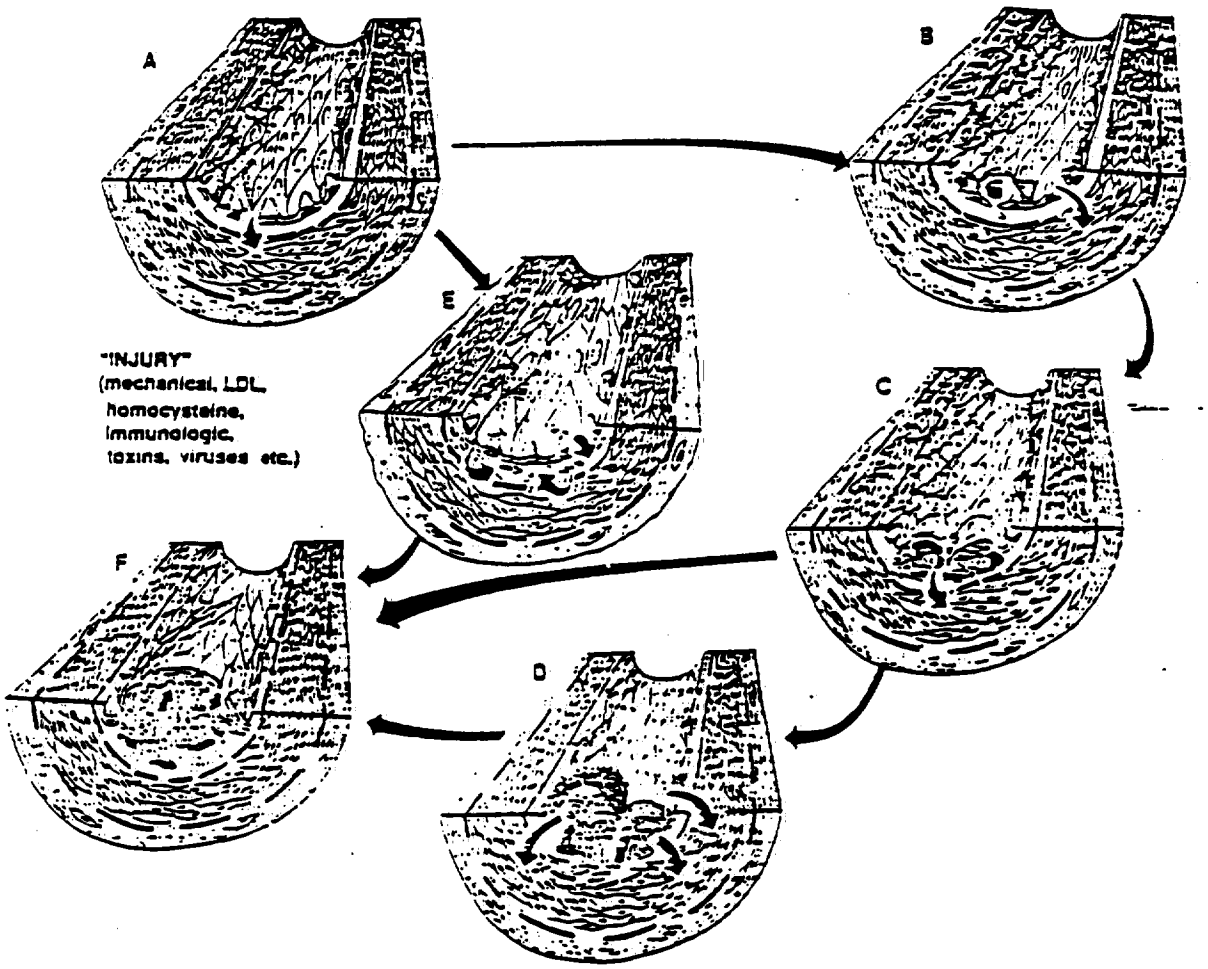
FIGURE 4.



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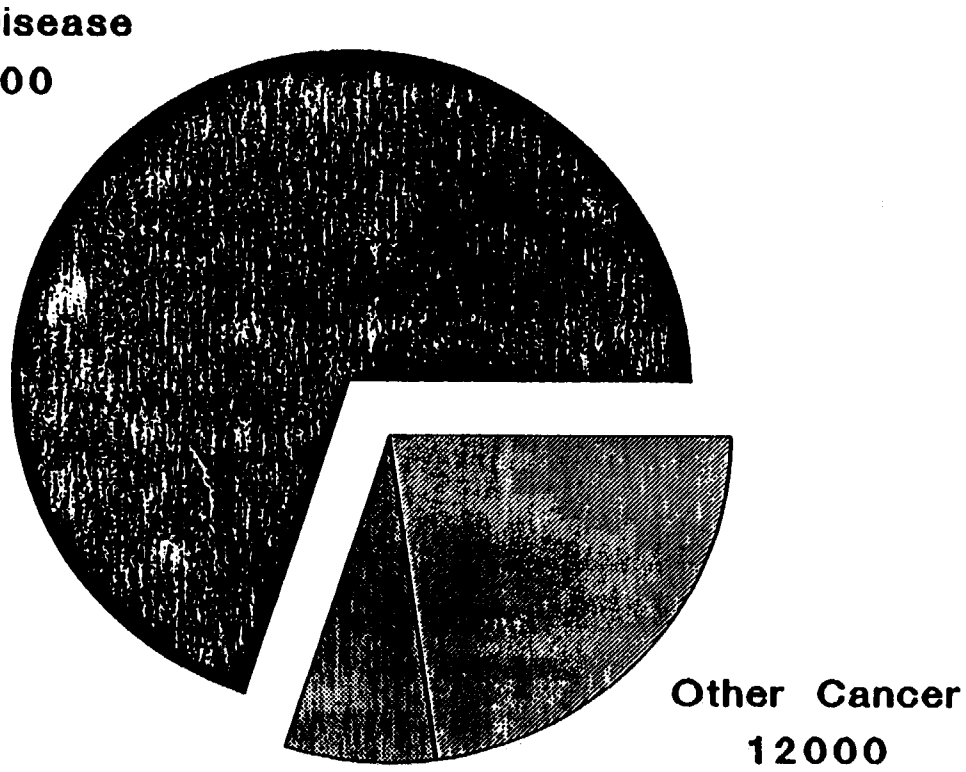
Deaths from Passive Smoking

Total Deaths: 53,000



Source: Wells, 1988

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CHAPTER 7

EXPOSURE ASSESSMENT IN PASSIVE SMOKING

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Introduction

This chapter will discuss some of the factors involved in the assessment of exposure to indoor air pollution from tobacco smoke. Exposures to environmental tobacco smoke (ETS) have been assessed by questionnaires, personal air contaminant monitoring of ETS constituents, modeling of concentrations, and biological markers. (NRC, 1986) Most of the epidemiological studies of passive smoking and disease have relied on questionnaires relating to the presence or absence of a smoker at home, and have assumed that this is a good surrogate for total exposure to ETS. To the extent that nonsmokers are heavily exposed outside the home, e.g., the workplace, this surrogate exposure variable will not differentiate well between a more exposed and less exposed group, and tend to cause epidemiologic studies of passive smoking and disease to find no effect or to lack statistical significance.(Repace & Lowrey, 1990) For this reason, several workers, in assessing risk from passive smoking, have attempted to correct for exposures outside the home by adjusting for the finite urinary cotinine concentrations in those who have reported "no exposure" to ETS. (NRC, 1986; Wells, 1990) No studies have yet been performed which yield a national probability sample of exposures to ETS. Thus, all attempts to assess exposure in individual epidemiological studies and otherwise have relied on some assumed paradigm of exposure. This chapter will discuss the evidence for exposure, and emphasize the insights which derive from a modeling approach.

Exposure to ETS occurs when an individual occupies a microenvironment which possesses an ETS concentration. A dose is said to occur when the individual breathes the concentration. An individual's total exposure to ETS is the time-weighted sum of the individual microenvironmental ETS exposures encountered during the day's activities.(Repace et al., 1980). The dose of ETS will be affected by the individual's respiration rate during the exposures. The dose of various ETS constituents to the body will be determined by their relative rates of absorption and removal. The amount of ETS inhaled is given by the product of the individual's respiration rate during exposure, the ETS concentration in the building, and the duration of the individual's stay in that microenvironment. In

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equilibrium, the ETS concentration is directly proportional to the product of number of smokers, smoking rate, and emissions per cigarette, pipe, or cigar, and is inversely proportional to the product of space volume and removal rate. (Repace, IARC, 1987)

In the epidemiologic studies of passive smoking and lung cancer, exposures are typically estimated on the basis of a questionnaire which assesses smoking status, and typically ask simple questions of the sort: "if you are a nonsmoker, do you live with, or work with, or have regular contact with persons who are nonsmokers?" (NRC, 1986) Some studies assess past exposure history and spouses' smoking rate as well. This kind of question, though useful, is not likely to be fully reliable or precise, particularly for non-domestic exposures. (NRC, 1986; IARC, 1987) On the other hand, it has been shown that those nonsmokers who report exposure to ETS at home tend to have higher non-domestic exposures as well.(NRC, 1986; Wald, 1986) Those individuals who have exposures both at home and at work appear to have higher exposures than those who are exposed at home only or at work only, as reflected by their urinary cotinine excretion. (Riboli, et al., 1990) Riboli et al. (1990) report data from a ten-country study of 1369 women, showing that when appropriately questioned, nonsmoking women can provide a reasonably accurate description of ETS exposure.

Ideally, the health effects of ETS might be assessed by quantifying the time-dependent exposures for each of the several thousand compounds in tobacco smoke and defining dose-response relationships for these compounds in producing disease, both as isolated compounds and in various combinations. However, the enormity of this task has led to simpler approaches which attempt to use measures of exposure to individual smoke constituents as estimates of whole smoke exposure. For this reason, exposures to ETS are often assessed using markers of the vapor phase or particulate phase. Although biological markers show promise as measures of exposure (and dose), they also have limitations. Another consideration is duration of exposure. For chronic diseases such as cancer, average exposures occuring over a year or lifetime are of greater importance than short-term exposures.(SG, 1986)

The two most promising atmospheric markers for ETS are respirable suspended particles in the size range $\leq$3 um (RSP) and nicotine.(NRC,1986; SG,1986; IARC,1987) A majority of field studies have used RSP as an indicator of exposure to ETS because of the substantial emission of RSP in indoor spaces from tobacco combustion. ETS is the dominant contributor to the indoor levels of RSP. The total RSP, as measured by personal monitors, has been found to be substantially elevated for those who report exposure to ETS relative to those who report no exposure. Both air monitoring and modeling clearly indicate that RSP concentrations will be elevated over background levels in indoor spaces when even low smoking rates occur.(NRC, 1986) Although lacking specificity

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for tobacco smoke, the prevalence and number of smokers correlates well with RSP levels in homes and other enclosed areas.(SG,1986) RSP is the single largest component of ETS by weight, and RSP is currently the best and most-utilized general category of air contaminants to represent ETS.(NRC,1986) A recent study of week-long averages of RSP and nicotine in about 100 homes with smokers in New York State showed an RSP-to-nicotine ratio of about 11:1, above a background of about 20 ug/m^3.(Leaderer, 1990) Similar results were obtained in a survey of 21 commercial buildings by Miesner, et al. (1989), who found a RSP-to-nicotine ratio of about 10:1 for workday averages, above a background of about 23 ug/m^3.

Biological markers in body fluids have also been used for validating self-reports of exposures to ETS. For example, Haley et al.(1989) and Cummings et al. (1990) found that cotinine levels in the urine of those who reported exposure to ETS were more than twice as high as those who denied having been exposed. Nicotine and its metabolite cotinine, which derive exclusively from tobacco products, are the most important markers. Almost all nicotine shifts from the particulate phase in mainstream and fresh sidestream smoke to the vapor phase in ETS. Nicotine and cotinine can be quantified in saliva, blood, and urine. Generally, the mean concentrations of nicotine and cotinine in plasma or urine of nonsmokers exposed to ETS under natural conditions is about 1 percent of the mean values in smokers, (NRC,1986) reflecting the fact that smokers are present in nearly all environments, including most workplaces, restaurants, and even in many vehicles, making it almost impossible for nonsmokers to avoid exposure to ETS.(SG,1986)

A. Sources of ETS

In 1986, an estimated 50 million US smokers aged ≥17 yrs smoked about 584 billion cigarettes annually. (NRC, 1986; Tobacco Institute, 1987) They consumed an additional 3.2 billion cigars, as well as an estimated 24.4 million pounds of tobacco for pipes and hand-rolled cigarettes.(NRC, 1986) The average US cigarette smoker smokes 32 cigarettes per day at a rate of 2 cigarettes per hour and emits about 22 mg of RSP per cigarette.(Repace, IARC, 1987) Since the average person spends about 90% of the time indoors, an estimated 12,000 metric tons of RSP are emitted into US indoor microenvironments each year from cigarette smoking alone. Assuming cigars produce 3 times as much RSP as cigarettes and that pipes produce as much RSP as a cigarette, (Repace and Lowrey, 1982) where pipes and hand-rolled cigarettes are assumed to contain 1 g of tobacco, then all cigars are estimated to contribute as much RSP indoors as 11 billion cigarettes, while all pipes and hand-rolled cigarettes are estimated to contribute as much as 15 billion regular cigarettes. This increases the estimated total RSP generated in US indoor microenvironments from all cigarettes, pipes, and cigars to nearly 13,000 metric tons per year. As exemplified by data from EPA's TEAM study, ETS predominates over

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other sources of RSP indoors (see Fig. 1.)

Although the percentage of the population that smokes has declined from nearly 50% in the 1960's to about 30% presently (OSH,1988), the percent of smokers who are heavy smokers has increased steadily over the past 30 years; thus although the percentage of smokers has gone down, the increase in smoking rate may tend to offset that trend towards lowering nonsmoker exposure to ETS.(NRC,1986).

B. Indoor air transport of ETS

Nonsmokers are exposed to ETS in indoor spaces. The determinants of these enclosed-space exposures include smoking occupancy, source air-contaminant emission characteristics, source use, building characteristics, space volume, infiltration or ventilation rates, efficiency of air mixing, surface sorption, chemical transformation, and the efficiency of air cleaning equipment. The interaction of these variables in determining the resultant concentrations of ETS has been evaluated in both controlled laboratory settings and in field studies within the theoretical framework of the mass-balance equation. The mass-balance equation may be applied to tobacco smoke either as an equilibrium model (time-independent) or as a dynamic model (time-dependent). Dynamic and equilibrium models are useful in laboratory studies; equilibrium models are best suited to evaluating and predicting ETS concentrations in field studies, particularly when average concentrations over a period of a workday or longer are of interest. (NRC,1986)

Laboratory and field studies typically utilize some form of a single-compartment equilibrium model to evaluate the input parameters of the mass-balance equation, to evaluate field study data, and to project RSP concentrations from ETS indoors. These studies have reduced the general single-compartment mass-balance equation to the following simplified form:

$$C_{eq} = G[m(N_v + N_s)V]^{-1} \qquad (1),$$

where C_{eq} is the equilibrium concentration of ETS-generated RSP in a space, expressed in units of micrograms per cubic meter (ug/m^3), G is the RSP generation rate from tobacco combustion in units of micrograms per hour (ug/hr), N_v is the ventilation or infiltration rate in units of airchanges per hour (ach), N_s is the loss rate of RSP due to surface removal in a space in air changes per hour, V is the volume of the space in cubic meters (m^3), and m is the mixing rate (Repace, IARC, 1987) expressed as a fraction. The above model assumes no air-cleaning devices, either in the space or recirculated air; Leaderer (1984) has given a detailed review of this model. Under laboratory conditions, these input parameters can be controlled and evaluated. In conducting field studies or in estimating past RSP levels indoors, the values on the right side

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of eq.1 have to be determined from available data. This equation assumes equilbrium conditions, and to the extent that any of the generation or removal terms are intermittent (e.g. smoking rate) or variable (e.g. ventilation rate), errors are introduced. (NRC,1986)

According to the National Research Council (1986) the most extensive use of the mass-balance equation for assessing RSP levels due to ETS in occupied spaces has been by Repace and Lowrey (1980), who proposed and applied in field observations a condensed version of the mass-balance equation for estimating RSP exposures due to ETS in a variety of indoor microenvironments. Their model is:

$$C_{eq} = 650\ D_s/N_v \qquad (2),$$

where C_{eq} is the equilibrium concentration of RSP due to ETS in units of micrograms per cubic meter, D_s is the density of active smokers (burning cigarettes) observed in a space per 100 m^3 over the sampling time, and N_v is the ventilation or infiltration rate in ach.(NRC,1986) The constant term (650) is calculated from a standard set of assumed conditions for smoking rates, RSP emission rates, mixing factors, ventilation rates, and sink rates. These standard sets of conditions are derived largely from experimental data and building standards. In applying equilbrium mass balance models such as eq.(2), gathering data on easily measured input parameters such as smoking rates or volume can substantially reduce the variablity of the estimated RSP levels.(NRC,1986) Eq. 2 was validated under controlled experimental conditions in real world settings, and was found to predict the equilibrium values of ETS within a high degree of accuracy in exposure chambers using real smokers.(Repace & Lowrey,1980, 1982, Repace, IARC, 1987) Further, the predictions of the model were found to be consistent with RSP levels from ETS measured in the field. However, the NRC stated that additional field testing of eq.(2) as well as a better understanding of the variability of the input parameters was needed.(NRC,1986) In 1987, Rickert et al.(1987) tested a key theoretical assumption regarding the ratio between the effective and ventilatory air exchange rates in the constant term in eq. 2 (Repace, IARC, 1987) and found that the model explained 87% of the variation between observed and predicted values for RSP concentrations from ETS in their experiments.

More recently, Repace(IARC,1987) has published a derivative of eq.2 which incorporate advances in understanding. Eq.(2) assumes a steady generation of tobacco smoke, which is generally only valid when 3 or more smokers are present in a space. For less than 3 smokers, it represents an upper bound. It is also limited for modeling purposes by being based on the room density of active smokers. The derivative equation is based on the room density of habitual smokers (number of habitual smokers per unit space volume). Thus, the presence of an archetypical "habitual" smoker (i.e., one who is assumed to smoke at an average rate of 2

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cigarettes per hour at 10 minutes per cigarette, with an emission factor of about 22 mg of SS RSP per cigarette) is the modeling parameter rather than the room density of burning cigarettes. (IARC, 1987) This derivative equation is given as follows:

$$C_{eq} = 217\ D_{hs}/N_v \qquad (3),$$

where C_{eq} is the equilibrium concentration in units of micrograms per cubic meter, D_{hs} is the number of habitual smokers per 100 cubic meters of space volume, and N_v is the number of space air changes per hour. Eq. 3 assumes that tobacco smoke concentration is in equilibrium, which occurs when the rate of generation equals the rate of removal, and the concentration is in a steady state. This assumption presumes three or more smokers, since the average smoker smokes three cigarettes per hour and takes ten minutes to smoke a cigarette. This means that with three smokers in a room, a cigarette will always be burning. (During growth, eq. (3) becomes $A_g = Ceq\ (1-exp-tN_v)$; during decay, $A_d(t \geq T) = A_g\ exp^{-tN_v}$, where T is the smoking duration. (Repace, 1987) A more detailed description of the derivation and validation of eq. 3 and the uses and limitations of these models is given by Repace, (IARC, 1987, chapter 3).)

If the number of habitual smokers being modeled is only 2 or 1, steady-state conditions no longer apply, and other simple approximations have been suggested, (Repace (IARC, 1987) in lieu of using exact time-dependent growth and decay models. A one-smoker-approximation model proposed by Repace (IARC, 1987) agrees very well with the instantaneous predictions of an exact computer simulation performed by Rickert (1988), but significantly underestimates newly available field data, which represent time-averaged concentrations. On the other hand, by contrast, eq. (3) for less than 3 smokers represents an upper bound to the ETS concentration, and as is illustrated below, produces reasonable agreement with, and provides useful insights into, the analysis of field data.

For example: As part of the the Harvard 6-City study of indoor and outdoor air quality, Spengler and colleagues (1981) collected RSP samples in 55 homes in 6 cities between May 1977 and April 1978. The number of smokers living in each home was recorded. The quantity of tobacco smoked was not reported, nor were the number of hours each smoker spent in the home or air exchange rates measured. The daily average "background," or mean indoor RSP level in the homes of nonsmokers was found to be about 24 ug/m^3; using regression analysis, the authors estimated that the average impact of a single smoker (a composite averaged over both sexes) on 24-hr average RSP levels from ETS in a residence was about 20 ug/m^3 above background. On average, two such habitual smokers would make about 40 ug/m^3 above background (24-hr average), and so forth. Added to a background of 24 ug/m^3, this yields a daily average RSP concentration for one smoker homes of 44 ug/m^3, and for two-smoker

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homes of 64 ug/m^3. What does eq. 3 predict?

Although the air exchange rates were unknown, Fig. 2 shows a histogram of the frequency of occurrence of various air exhange rates (called infiltration rates) during the heating season for typical middle income housing (R. Grot, personal communication) for 266 homes in 14 cities around the US in 1978 (SG,1986). Occupants were asked to keep windows and doors closed during the tests. Under these conditions, the mean air exchange rate found was 1.1 $\pm$ 0.9 ach (Grot & Clark, 1979); this value is likely to be somewhat lower than a full seasonal average with no restrictions on door and window openings.

The smoker density for a one-smoker home of volume 340 m^3 has been given by Repace and Lowrey (1985) as D_{hs} = 0.29 habitual smokers per 100 m^3. Similarly, for a two-smoker home, D_{hs} = 0.58. In the absence of information on air exchange rates, let us assume, from Grot and Clark (1979), a rate, N_v = 1.1 ach. Then eq. 3 predicts a value of C_{eq} = 217 x 0.29/1.1 = 57 ug/m^3 during smoking, for a one smoker home, and 114 ug/m^3 for a two-smoker home. From table A1 for time budget studies in Repace and Lowrey (1985), averaged over employed men and women, and homemakers, the average amount of time spent awake in the home, (allowing for 8 hrs of sleep per day) is about 7.9 hours per day. Converting our calculations to a 24-hr average and adding a background of 24 ug/m^3, yields an estimated 57 x 7.9/24 + 24 = 43 ug/m^3 for a one-smoker home, and 114 x 7.9/24 + 24 = 62 ug/m^3 for the two smoker home, in good agreement with the values of 44 ug/m^3 and 64 ug/m^3 from the 6-City study above. A comparison of the predictions of eq. 3 with 17 months of RSP data on 55 homes in 6 Cities (Spengler, et al., 1981) is given in fig. 3. This example illustrates the utility of models in estimating nonsmokers' domestic exposures to ETS.

As a second example, consider the measured aerosol mass concentration in a 700 m^3 (25000 ft^2 floor area) office with one smoker (smoking rate not reported), and a measured air exchange rate of 1 ach (see Fig. 4); the large impact on the office aerosol concentration caused by smoking is apparent by comparing the daytime and evening RSP concentrations.(IARC, 1987) The predictions of eq. 3 for D_{hs} = 1 smoker per 7 hundred cubic meters and N_v = 1 ach yields C_{eq} = 31 ug/m^3; with an 18 ug/m^3 background added, the predicted RSP level is 49 ug/m^3, in good agreement with observations (fig 4). It is clear from fig. 4 and also from models, that ETS can be very persistent in indoor environments: at an air exchange rate of 1 ach, it takes 3 hrs for 95% of the smoke from 1 cigarette to be removed (Repace, IARC, 1987)

A third example, where more information is available on the smoking rates, home volumes and air exchange rates, is provided by the data obtained in the NYSERDA study of weekly average residential aerosol concentrations in 141 homes with

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smokers.(Leaderer, et al., 1990) The measured weekly average RSP levels were 43 ug/m3 in the smoking homes, the background levels averaged 16 ug/m^3 in the nonsmoking homes, the average air exchange rates were 0.54 ach, the average house volumes 353 m3, the average number of cigarettes smoked per week was 99.3, and the average number of hours of smoking per day is calculated at 7.1 hrs/day assuming 2 cig/smoker-hr (Repace and Lowrey, 1980). From this data, using eq. 3 as before, we calculate R = 217 x 0.28/0.54 x 7.1/24 + 16 = 49 ug/m^3, in reasonable agreement with the observed average of 43 ug/m^3, but higher, as expected. Thus, although eq. 3 for less than 3 smokers represents a simplified upper-bound approximation, it has utility in producing estimates which are reasonably consistent with field data, and has the advantage that it is simple to use. However, since none of these studies were specifically designed for model validation, further comparisons with field data are important as new data sets become available.

A sampling of whole-building air-exchange rates in 8 large federal office buildings in 7 states with different climates is shown in Fig. 5, and these generally approximate the ASHRAE 62-81 ventilation standards for offices (20 cfm per occupant, equivalent to 0.84 ach, for smoking buildings), on average, although there are some buildings significantly lower. A recent EPA study of air exchange rates in 6 buildings (3 new, 3 old) did not show significant differences between the new (.5 ach) and old (.5 ach) buildings' airchange rates, although for a given building nighttime measurements tended to be lower. (Sheldon, et al.,1987) Recent research has revealed several interesting factors in large office building air exhange. There are many pathways for floor-to-floor air communication, particularly return air shafts, where the existence of such pathways can cause a building's air exchange characteristics to closely approximate those of a single large open space; it does not require unusual numbers or sizes of openings to create these conditions,(A.Persily, personal communication; Persily and Grot,1986) a condition for which eq. 3 was designed. This implies that ETS may diffuse throughout a large office building, exposing nonsmokers even in private offices. Nicotine measurements in office buildings support this observation. (Williams, et al., 1985; Vaughn and Hammond, 1989)

In summary, limited field tests of the general equilibrium model, in which some of the input parameters are measured and others are estimated from either chamber studies or building codes, have predicted RSP levels reasonably well over a wide range of values of input parameters. It is clear that both models and observations based on personal monitoring or area monitors in various microenvironments yield consistent results: RSP levels when smoking is allowed will result in substantial increases over RSP levels in nonsmoking occupancy.(NRC,1986)

C. Tobacco Smoke and Ventilation

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Because of widespread public smoking, many buildings are contaminated with tobacco smoke combustion products. Many building owners and managers have assumed that ventilation is a viable control mechanism for the clouds of smoke that are generated by cigarettes, pipes, and cigars. In particular, the ventilation standards proposed by ASHRAE (the American Society of Heating, Refrigerating, and Air Conditioning Engineers) are often thought to afford adequate control of tobacco smoke. However, ASHRAE standards are not health-based standards designed to limit cancer risk or eye irritation to levels acceptable to nonsmokers. They are designed only to limit dissatisfaction with tobacco smoke odor to a maximum of 20% for "visitors" (a test panel consisting of 50% smokers and 50% nonsmokers) to a building where smoking occurs. Currently ASHRAE recommends 20 cubic feet per minute per occupant (cfm/occ) for this purpose. Providing ventilation adequate to control cancer risk has been estimated to require 5400 cfm/occ, an unrealistic ventilation rate.(Repace & Lowrey, 1985)

Air cleaners have three fundamental problems. One, most air cleaners do not scrub gases from the air, and many of the harmful tars appear in the gases. (Pritchard, 1990) Two, air cleaners cannot remove smoke which encounters the nonsmoker before it reaches the air cleaner. Three, even air cleaners which are close to 100% effective in removing particles which reach them must process hundreds of room air volumes per hour to reduce cancer risk to an acceptable level.(Repace & Lowrey, 1985; Repace, 1989a) Separation of smokers from nonsmokers within a space will expose nonsmokers to smoke which diffuses from the smoking area. Separation on the same ventilation system will reduce peak concentrations to which nonsmokers are exposed, but will expose nonsmokers to smoke recirculated by the ventilation system.(Repace, 1989; Repace and Lowrey, 1987)

The foregoing considerations demonstrate that source control, i.e., removing the smoking from the air volume containing nonsmokers, is the only viable control option. Source control adequate to protect nonsmokers takes two forms: separation of smokers from nonsmokers on separate ventilation systems, or restriction of smoking from the building. (USEPA, 1989) Separation of smokers in a designated smoking area exposes them to much higher levels of exposure to ETS, and may significantly increase an already considerable risk from active smoking.(Repace, 1989b)

D. Measured concentrations of ETS constituents:

RSP: Both field studies (Table 1) as well as chamber studies have demonstrated that tobacco combustion has a major impact on the mass of suspended particulate matter in occupied spaces in the size range <2.5 um, defined here as RSP. RSP is a major component of ETS. Even under conditions of low smoking rates, easily measurable increases in RSP have been recorded above background levels. The term RSP, however, encompasses a broad

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range of particulates of varying chemical composition and size emanating from a number of sources (outdoors, cooking indoors, kerosene heaters, etc.)(NRC, 1986) The apportionment of RSP indoors depends primarily on the presence of these other sources. However, in western society, there are few indoor sources generating concentations which approach in strength those due to ETS. There appears to be little variability between brands of cigarettes or tobaccos for RSP emissions, although cigars will produce greater emissions than cigarettes. Thus, it may be inferred from Table 1 that from a comparison of smoking and nonsmoking buildings, the bulk of the RSP found in buildings where there is smoking is due to ETS. For example, by comparison of the data of First (1984), Leaderer, et al (1986) and Repace and Lowrey (1980,1982) for a total of 42 smoking buildings and 21 nonsmoking buildings, the weighted average RSP level in the smoking buildings is 262 ug/m^3, while in the nonsmoking buildings it is 36 ug/m^3, suggesting that about 85% of the indoor RSP levels in those buildings is due to ETS. Most of the buildings involved were public access buildings. Hammond et al. (1988) measured personal exposures to RSP in several hundred railroad workers. Mean calculated ETS-derived RSP exposures for railroad office workers averaged over 90 ug/m3; by comparison, all other sources of RSP for these diesel-exhaust exposed workers averaged 39 ug/m3. The U.S. Department of Transportation (1990) measured concentrations of RSP in the smoking section of a random sample of 69 smoking and 23 nonsmoking flights. Nonsmoking flight attendants must work in the smoking sections on aircraft. Levels of RSP on the smoking flights averaged 175 ug/m3, whereas measurements in the same section of the aircraft on nonsmoking flights averaged 35 to 40 ug/m3.

Figure 6, (IARC, 1987) a plot of the data of Repace and Lowrey (1980, 1982) illustrates the large impact of smoking on RSP levels; smoking data points 'A' thru 'T' encompassed a wide variety building microenvironments,including 10 restaurants, 3 cocktail lounges, 3 bingo games, 2 dinner-dance halls, 1 bowling alley, 1 sports arena, 1 hospital waiting room, and a residence during a dinner party. Studies of the dispersion of RSP from ETS in US homes showed at most a factor of 2 difference among various rooms in residences, averaged over 24 hrs. In a setting such as a work environment, where the average exposure is several hours, ETS would be expected to disseminate throughout the airspace where smoking is occuring.(SG, 1986) Although most people spend approximately 90 percent of their time in just two microenvironments (home and work), important exposures can also be encountered in other microenvironents, e.g., in transit, which accounts for 0.5 to 1.5 hrs per day for most people..(SG, 1986) Exposures on aircraft can also be considerable. (Repace and Lowrey, 1988; USDOT, 1989)

BENZENE: Wallace (1989) in reporting the results of EPA's TEAM study with respect to the benzene exposure of the population, found that ETS was a significant source of population benzene exposure, accounting for about 5% of total nationwide exposure. Wallace

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reported that workplace exposures for nonsmokers not exposed to ETS at home, but who report being exposed to ETS more than 50% of the time at work showed significantly higher benzene concentrations than those who report exposure to ETS less than 50% of the time. Wallace estimates that ETS-benzene exposures are about equal at home and at work.

NICOTINE: Leaderer and Hammond (in press) measured vapor phase nicotine and RSP concentrations in 96 residences. Vapor phase nicotine measurements were found to be closely related to number of cigarettes smoked and highly predictive of RSP generated by tobacco combustion. The mean RSP background in the absence of measurable nicotine was found to be 15.2 ± 7 ug/m3. The mean RSP value in the presence of nicotine was 44.1 ± 30 ug/m3. Weekly mean nicotine concentrations in the residences was 1.1 ug/m3.

Stillman et al. (in press) measured weekly average nicotine concentrations using the method of Leaderer and Hammond (above), in 9 (F. Stillman, pers. comm.) university offices. Concentrations averaged 2.1 ug/m3. After a smoking policy was implemented, the nicotine levels decreased by 95%. Vaughn and Hammond (1990) measured weekly average nicotine concentrations in offices in a modern office building using both active and passive samplers. Before the smoking control policy, nicotine vapor concentrations at nonsmokers' desks were about 2 ug/m3, and were reduced by 95% after a smoking policy was implemented, in good agreement with the findings of Stillman, above. Hammond et al. (1988) measured nicotine and RSP in two employee smoking lounges at the University of Massachusetts. RSP levels varied between 220 and 350 ug/m3 during smoking, with associated nicotine levels from 40 to 70 ug/m3. After charcoal-filter air cleaners were installed, nicotine levels were virtually unchanged, and RSP levels varied between 100 and 310 ug/m3.

A study of personal exposures to airborne nicotine in 4 US office workers showed about a 0.1 mg mean exposure (mean personal nicotine concentration of 15 ± 9 ug/m^3, daily workday average, times a 0.8 m^3/hr inhalation rate times an 8-hr workday). The nonsmokers were exposed to the smoke of a co-worker who smoked 9 cigarettes per workshift, about half the rate of the average US smoker. (Hammond et al.,1987)

E. Exposure of nonsmoking populations to ETS

In the general population (both sexes) aged ≥ 17 years in 1980 (160,798,000 persons), a majority has smoked at some time: 32.6% were current smokers, and 21.3% were exsmokers, while 46.1% had never smoked (see Table 2). Among current 1980 smokers, 53% were male, and 47% were female, with some race- and gender-specific differences : white males, 35.9%, black males, 42.0%; white females, 29.3%, black females, 29.7%. (R. Wilson, NCHS, personal communication) In terms of the population at risk, both lifelong

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nonsmokers and former smokers, 66.7% of the adult population and the overwhelming majority of children are potentially at risk from involuntary exposure to ETS (in 1970, Bonham and Wilson (1970) found in a national probability sample of children, that 62% of US homes with children contained 1 or more smokers). Exposure to various subpopulations or individuals, however, may vary considerably. For example, the prevalence of smoking among subgroups of the population who proscribe smoking on religious grounds (such as Mormons and Seventh-Day Adventists) is much lower: for example, in 1980, only 1.7% of Seventh Day Adventist men and 0.5% of Seventh Day Adventist women reported current smoking, although 35% of the total were exsmokers. The incidence of lung cancer -- a disease for which the majority of cases occur in smokers -- among SDAs is 21% of that in the general population. Thus, SDA homes would be, in general, expected to be ETS-free.

The microenvironments of importance for exposure to ETS will be those where the population spends the bulk of its time. As Table 3 (Ott, 1981)(based on 1972 data) shows, employed men spend an estimated 56% of their time at home, and 28% of their time at work, for a total of 84% of the time at home and at work; employed women spend 64% of their time at home, and 22% of the time at work, for total of 86% of the time at home and at work; while homemakers spend 85% of the time at home. When time spent in other peoples' homes and in non-work places of business are added in, the population averages about 88% of its time in homes and workplaces. These sites, therefore, must, on average, predominate as potential sites for exposure to ETS for the general nonsmoking population. A UK study of exposure to ETS in 20 nonsmoking men whose wives smoked showed that 78% of the men's reported hours exposure came from outside the home; by contrast, 90% of the ETS exposure of 101 nonsmoking men whose wives did not smoke was reported to come from non-domestic microenvironments. (Table 4). Since the second largest source of time spent by men is in the workplace (Table 3), this suggests the workplace may be the major source of exposure for nonsmoking men.

Cummings et al (1990) studied the prevalance of exposure to ETS in 663 never- and ex-smokers who attended a cancer clinic in Buffalo, N.Y. in 1986, by questionairre and urinary cotinine level. 76% reported exposure to ETS in the 4 days preceding the interview, while 91% had detectable urinary cotinine levels. Reported exposure locations in order of frequency were workplace (28%), home (27%), restaurants (16%), private social gatherings (11%), in transit (10%), and in public buildings (8%), (total of 100%). 77% of subjects reported being exposed to tobacco smoke at work, while 22% of the subjects lived with a smoker. In a second study, Cummings et al. (1989) reported on 380 never smokers from the same study: A total of 87% reported exposure to tobacco smoke at work. 24.3% of the men reported spousal smoking, whereas 94.7% reported workplace exposure; significantly, when asked to rate the severity of exposure, on a scale where spousal smoking was normalized to 1,

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severity of workplace exposure was rated 5. 66% of women reported spousal smoking, whereas 83.5% reported being exposed to smoking in the workplace. The women studied rated the severity of spousal smoking at about 30% higher than workplace exposures.

Coultas et al. (1990), in a pilot study of 15 nonsmokers in Albuquerque, N.M., exposure questionnaires and saliva, urine, and personal air samples were obtained pre- and post- workshift. Nicotine and cotinine levels were quantified, as were atmospheric nicotine and RSP samples. Statistically significant correlations were obtained between RSP and nicotine and total reported hours of exposure; between nicotine and total number of smokers, total hours of exposure, and postshift urinary cotinine; between urinary cotinine and total hours of exposure; and between salivary cotinine and total number of smokers. Objective evidence of exposure to ETS was obtained in various workplaces. Spengler et al.(1985) and Sexton et al. (1984) demonstrated by personal monitoring of RSP and the use of time-activity questionnaires that exposures to ETS both at home and at work are significant contributors to personal exposures.

A survey of exposure to ETS in a California population subscribing to a health-maintainance plan indicated that 63% of nonsmokers surveyed reported exposures to tobacco smoke (Friedman, 1983); this occurred despite the fact that in the 1980's California has has been in the forefront of restrictions on smoking in public, with 44% of its population currently living in communities that have enacted workplace smoking restrictions.(SG, 1986) Garfinkel (1981), in a study of 176,000 nonsmoking US women (1960-1972), found 72% had smoking husbands. Kabat and Wynder (1986), in a recent study of 215 sixty-year-old US women nonsmokers, found that 65% were exposed at home and 67% reported exposure at work, averaged over adulthood. Studies of the concentration of nicotine and cotinine in the body fluids of nonsmokers report similar results (Table 4); Jarvis & Russell, (1984) showed that in a study of about 100 UK nonsmokers, only 12% of the subjects had undetectable cotinine levels. Moreover, in the latter study, surprisingly, nearly 50% reported no exposure, suggesting that ETS permeates indoor atmospheres to such an extent that many nonsmokers are unwittingly exposed. This is borne out by a study of 46 US infants, 40% of whom were reported by their mothers to be unexposed to ETS, but only 20% had undetectable urinary cotinine levels.(Greenberg, 1986) In a third UK study (Wald, 1986) of urinary cotinine in 221 nonsmokers, the 20% who reported no exposure had mean urinary cotinine levels which were 21% of the remainder of the group who reported exposure.

The foregoing illustrates that exposure to ETS is very widespread in the population, even among those nonsmokers who believe themselves to be unexposed, however it tends to be greater in those who say they are exposed at home, possibly indicating a greater tolerance for ETS among men with nonsmoking spouses.

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Although there have been numerous measurements of ETS concentrations in various indoor settings, these data do not represent a comprehensive description of the actual distribution of ETS exposures in the US population. However, additional data on the distribution of smokers in the nonsmokers' environment as well as the distribution of ETS levels in that environment, are needed in order to characterize the actual ETS exposure of the population. In the absence of such data, population exposures can be estimated by models or by extrapolation from biological markers from existing studies. (SG, 1986; IARC, 1987)

In summary, exposures to ETS can be assessed by personal air contaminant monitoring, modeling of concentrations based upon air sampling, time-activity patterns, and questionnaires, or upon biological markers. The two best methods at present are based upon the biological markers, nicotine and its metabolite, cotinine, which are present in the saliva, plasma, and urine of active and passive smokers, and upon atmospheric markers such as nicotine in the vapor phase and RSP from the particulate phase of ETS, the latter of which has been used in many field studies because of the substantial emission of RSP from tobacco combustion. In US, ETS is generated by 50 million smokers, who smoke the equivalent (including pipes and cigars) of 610 billion cigarettes annually. Although the number of smokers has been declining, the percentage of heavy smokers has been increasing. There are models in use, based on the mass-balance equation, and validated both under laboratory and limited field conditions, which can predict the concentrations of RSP from ETS to a reasonable degree of accuracy. Application of such models, together with field studies of RSP concentrations and sociological studies, has suggested that exposure to ETS is very widespread in the population. Environmental tobacco smoke is not readily controlled by either ventilation or air cleaning. Field studies of RSP in buildings where smoking occurs suggest that RSP from ETS contributes 80 to 90 percent of the particulate load during the period of smoking, and that it persists for long periods after smoking ends at typical building air exchange rates, thus prolonging nonsmokers' exposures. Available data suggest the workplace as a significant site of exposure to ETS.

F. Integrated exposure analysis

Exposure to ETS can be quantified either by atmospheric or biological markers. Of the latter, expired carbon monoxide, carboxyhemoglobin, plasma thiocyanate, plasma, urinary or salivary nicotine, and plasma, urinary, or salivary cotinine have been used to evaluate exposure to ETS. However, successful attempts to quantify the degree of exposure have been limited largely to measurements of nicotine and cotinine. Urinary nicotine is a sensitive indicator of recent ETS exposure, while cotinine appears to be the short-term marker of choice for epidemiologic studies. Nicotine and cotinine are the best markers currently available.

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Levels in body fluids may be elevated 10 or more times in the most heavily exposed groups compared with the least exposed groups. Mean levels of urinary nicotine and cotinine in body fluids increase with an increasing self-reported ETS exposure and with an increasing number of cigarettes smoked per day by active smokers. (SG, 1986) Coghlin, Hammond, and Gann (1989), in assessing current weekly ETS exposure in 53 nonsmoking volunteers by personal nicotine monitors, diaries, and questionnaires, found that the best predictor of total nicotine exposure was given by the formula hsp: the number of hours of exposure (h), times the number of smokers (s), times the proximity of those smokers (p), accounting for 83% of total exposure. A significant finding was that exposures derived from social situations (e.g. restaurants, bingo games, bars, and bowling alleys) (which are workplaces for some persons) may contribute significantly (34%) to total exposure.

Nicotine is found in measurable concentrations in the saliva and urine of most urban nonsmokers, and is present in higher concentrations in those with some recent exposure. Estimating the magnitude of the passive smoking dose is difficult, and it is of doubtful validity to extrapolate from the uptake of one marker to another. Over a period when one cigarette equivalent of carbon monoxide is absorbed, the dose of nicotine appears to be only between 1/10 and 1/3 of a cigarette equivalent. Similarly, under extreme conditions of indoor pollution, it has been calculated that a nonsmoker would inhale volatile nitrosamines equivalent to 10 nonfilter cigarettes or 35 filter cigarettes. (Hoffmann, IARC, 1987)

The average concentration of cotinine in the blood of habitual smokers is about 300 ng/ml, and is calculated to represent the consumption of about 36 mg of nicotine per day. On this basis, and on the assumption that formation of cotinine from nicotine and clearance from the body does not differ substantially from smokers to nonsmokers, present data suggest that average urban nonsmokers (in the UK) take in 0.2 mg of nicotine per day. (IARC, 1987) [.2 mg represents .6% of the smokers' dose] The highest plasma cotinine concentration observed in a nonsmoker corresponds to an approximate maximum dose of 2.5 mg of nicotine per day, 10 times higher, and 7% of the average smoker's dose. Recent studies of salivary cotinine in schoolchildren in the UK showed, in the case where both parents smoked, average concentrations just over 1% of the levels seen in heavy cigarette smokers. (IARC, 1987)

Although the ratio of nicotine to other tobacco smoke constituents differs in MS and SS smoke, nicotine uptake may still be a valid marker for total ETS exposure. Nicotine uptake in nonsmokers has been estimated in terms of cigarette equivalents from various studies to vary between 1/6 to 1/3 of a cigarette per day. The NRC reports various estimates of cigarette equivalents based upon cotinine in nonsmokers ranging from 0.1 to 1 cigarette per day, and utilizes a ratio of urinary cotinine in ETS-exposed nonsmokers (25.2 ng/ml) to that in active smokers (1826 ng/ml)

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yielding a 1.4% result.(NRC, 1986) [Assuming a usage of 32 cigarettes per day by habitual smokers based upon cigarette sales (Repace and Lowrey, 1980), this yields 57 ng/ml/cigarette, or 0.44 cigarette equivalents per day. Adjusting this by multiplying by the ratio of cotinine clearance in nonsmokers to that in smokers reported in one study, 49.7 hrs/18.5 hrs = 2.67, yields a higher value, 1.1 cigarette equivalents per day or 3.6% of the smokers' dose.] In summary, based upon the limited studies (none of which are a probability sample of US nonsmokers) of cotinine in body fluids of nonsmokers (see Table 5), nonsmokers appear to have of the order of 1% of the nicotine uptake of smokers. However, these estimates must be interpreted with caution; relative absorption of nicotine in smokers and nonsmokers may substantially underestimate exposure to other components of ETS. (SG,1986)

Alternatively, human exposure to ETS can be estimated using approaches similar to those used for other airborne pollutants. Measures of exposure to individual atmospheric smoke constituents can be used as estimates of whole smoke exposure. The accuracy of this approach amy be limited by changes in the composition of ETS with time and conditions of exposure. Although lacking specificity for tobacco smoke, the prevalence and number of smokers correlates well with RSP levels in homes and other enclosed areas. In the Harvard study of indoor air pollution in 6 cities, Spengler et al. and Sexton et al. demonstrated by the personal monitoring of RSP and the use of time-activity questionnaires that exposures to ETS at home and at work are significant contributors to personal exposures. In general, measurements in a large number of locations using measures of smoke generation such as the number of people smoking or the number of cigarettes being smoked have shown a definite relationship of smoke generation to particulate levels. In US homes, there are few other sources of RSP, and therefore, the relationships of RSP measurements to ETS are quite accurate.(SG, 1986)

Repace and Lowrey (1980) measured RSP concentration using a piezobalance in several public and private locations, in both the presence and absence of smoking. They then developed an empirical model utilizing the mass balance equation (Eq.2). Using both measured and estimated parameters as input to the model, they validated the model for predicting an individual's exposure to ETS.(SG, 1986) Kuller et al (1986) in a review of estimates of the nonsmoking population's exposure to ETS, observed that cigarette smoking is probably the single most important source of indoor RSP; that a higher percentage of nonsmokers appear to be exposed out of the home, usually at work (Friedman, 1983); and that modeling of RSP has estimated that the average exposure of the nonsmoking adult population to tars from ETS was 1.43 mg/day, varying from 0 to 14 mg (Repace and Lowrey, 1985). Kuller et al. (1986) in reviewing the latter estimate, observed that the ratio of average exposure in passive smoking to that in active smoking, was about 0.3%. This translates into 3% of the smoker' exposure for the most-exposed

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passive smokers, reasonably consistent with estimates based on doses from nicotine and cotinine, above.

Table 6 gives estimates of the probability-weighted exposures to ETS for US nonsmoking adults at home and at work, the two most-frequented microevironments.(Repace and Lowrey, 1985) Table 6 is derived from RSP concentration modeling based upon Eq.'s 2-5, and from assessments of exposure probability based on a limited national survey of top management and health officials concerning prevalence of smoking in the workplace in 3000 US corporations, large, medium, and small (29% response), and a national probability sample of the prevalence of smoking in homes with children (used as a surrogate for all homes). Exposure probabilities were a weighted average taken over the number of workers in white-collar and blue-collar occupations, and including the different exposure probabilities for white and blue collar workers. Air exchange rates and building occupancies were taken from ASHRAE Standard ventilation rate tables for white-collar workplaces (which were used as surrogates for blue-collar workplaces).

Table 6 estimates average the workplace ETS exposure probability at 63%, and the average estimated domestic ETS exposure probability at 62%, where the focus was on estimation of ETS exposures in the 1950's to mid-1970's, since these exposures were held to be of primary significance for the studies of passive smoking and lung cancer, given the long latency for lung cancer. Comparison of these exposure probability estimates to adult life ETS exposure histories taken by Kabat and Wynder (1986) for 215 60-yr old female nonsmokers, 65% at home and 67% at work, shows good agreement. Table 6 estimates a 0.45 mg/day RSP exposure for nonsmokers at home, (weighted for male and female time-activity pattern differences, and for respiration rate) corresponding to a 19 ug/m^3 24-hr average, in good agreement with results (19 ug/m^3 per smoker) published in the 6-City study.(Repace and Lowrey, 1985) Table 6 also estimates a 1.82 mg/day RSP exposure for workers, (again weighted for male-female time-activity patterns and for respiration rate) corresponding to about a 230 ug/m^3 workplace concentration, using ASHRAE Standard 62-73 for workplace occupancy and performing a weighted average workday for the different hours worked by men and women (Repace and Lowrey, 1985). This is in good agreement with the weighted average concentrations (262 ug/m^3) reported for ETS in public access buildings.

Riboli et al.(1990) in a 10-country collaborative study of exposure of nonsmoking women to ETS, examined the relationship between smoking by spouse and urinary cotinine levels as an indicator of exposure to ETS. Riboli et al.(1990) found that cotinine values were significantly higher for women exposed to ETS from the husband than from other sources; they also found that questionairres in epidemiological studies based upon self-reports of spousal smoking in fact identified a most-exposed population. A clear increase in urinary cotinine levels was found from the

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women who were exposed neither at work or at home, to women who were exposed both at work and at home, as suggested by the work of Repace and Lowrey, above.

In summary, exposures to ETS can be assessed by personal air or area contaminant monitoring, modeling of exposures, or by biological markers of ETS contaminants in body fluids. Using either the biological markers such as cotinine or the atmospheric markers such as RSP produces a consistent assessment of ETS exposure, i.e., of the order of 1% of that in smokers. The most-exposed individuals appear to have levels about ten times higher. Based upon limited data, the typical nonsmoker appears to carry a daily body burden of about 0.2 milligrams (mg) of nicotine. The cotinine-based estimates have the advantage that they reflect actual dose of an ETS constituent. They have the disadvantage that they do not reflect a wide distribution of target populations, are based mostly on UK ETS exposures, and may substantially underestimate exposures to other constituents of ETS. The RSP-based estimates have the advantage that they are model-based, can be used to estimate exposures in a variety of microenvironments, represent the great bulk of ETS carcinogens, and can be compared with atmospheric measurements of RSP. They have the disadvantage that they do not represent whole smoke exposure, and do not reflect absorbed dose. The greatest source of uncertainty is that neither cotinine nor RSP measurements are based on a national probability sample, and on an absolute scale, represent a limited amount of data. Nevertheless, the NRC(1986), the SG(1986), and IARC(1987) have found this data base acceptable for exposure assessment purposes. Estimates of the adult nonsmoking population's exposure to RSP from ETS suggest that the range of exposure is from 0 to 14 mg per day, with the population average put at 1.5 mg per day, where the peak-to-mean ratio is about a factor of 10, consistent with the biomarker-based findings.

Summary

1. Nonsmokers' exposures may be assessed by mathematical modeling, as well as by biomarkers such as nicotine or cotinine in body fluids or atmospheric indicators such as nicotine or RSP.

2. Despite limitations of the data base, mathematical models, biological and atmospheric markers have produced reasonably consistent assessments of nonsmokers' ETS exposure.

3. Exposure to environmental tobacco smoke is inadequately controlled by ventilation, air cleaning, spacial separation within a space, or on the same ventilation system.

4. Data indicate that ETS is a significant indoor pollutant of buildings, typically representing 80 to 90% of particulate indoor air pollution during smoking, and that nearly all nonsmokers carry a significant burden of tobacco combustion products in their body

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fluids.

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FIGURES AND TABLES FOR CHAPTER 6

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Particulate Levels Measured in Indoor Environments, Including Smoking and Nonsmoking Occupancy

Study	Type of Premise	Occupancy	Volume, m^3	Ventilation Type/Rate	Monitoring Type/Time	Concentrations Mean (range), $\mu g/m^3$	Comments
Brunekreef and Boleij, 1982	4 residences	NS	—	N/—	G/2 mo	55 (20–90)	TSP, repeat measures 0.2 mg
	7 residences	S = 1	—	N/—	G/2 mo	125 (60–250)	TSP sensitivity
	14 residences	S = 2	—	N/—	G/2 mo	152 (60–340)	TSP sensitivity
	1 residence	S = 3	—	N/—	G/2 mo	335 (—)	TSP sensitivity
	Outdoors	—	—	—	G/2 mo	— (41–73)	
Cuddeback et al., 1976	2 taverns	S = 5–40 NS = 5–260 T = 10–300	—	N,M/1–6 ach	G/9 h	446 (233–986)	TSP ventilation estimated
Elliot and Rowe, 1975	3 arenas	NS	—	—	G/24 h	55 (42–92)	TSP
	3 arenas	S T = 2,000–14,277	—	M/—	G/0.3 h	350 (148–620)	TSP
First, 1984	1 school	NS	—	M/—	P/—	20 (—)	TSP
	8 public buildings	S	—	N,M/—	P/—	260 (40–660)	TSP
Hawthorne et al., 1984	11 residences	NS	150–674	M/0.18–0.96	QCM1/5–15 min (over 6 h)	9–40 (—)	RSP, winter/summer—no sources
	8 residences	NS	150–674	M/0.26–1.98	QCM1/5–15 min (over 6 h)	12–46	RSP, winter/summer—sources[e]
	2 residences	S	150–674	M/0.27–1.47	QCM1/5–15 min (over 6 h)	96–106	RSP, winter/summer—sources[e] + cig.
Leaderer et al., personal communication	3 public buildings	NS	163–1,326	M/0.37–5.6[d]	G/4–21 h	17.8 (9.1–32.2)	TSP, repeat measures, all var.
	7 public buildings	1.7–4.57[b] T = 2–6	168–600	M/0.77–7.53[d]	G/2–24 h	205.1 (58–452)	Measured (160.0 peak)
Moschandreas et al., 1981	Outdoors	—	—	—	G/24 h	17.0 (—)	RSP, TSP also measured
	2 offices	—	—	—	G/24 h	16.8–20.2 (53 peak)	RSP, TSP also measured
	5 residences	NS T = 2–6	—	N/0.5–1.3 ach	G/24 h	19.4–4.01 (118.9 peak)	RSP, TSP also measured
	5 residences	S	—	N/0.5–1.3 ach	G/24 h	36.9–99.9	RSP, TSP also measured
Nitschke et al., 1985	Outdoors	—	—	—	G/168 h	11.3 ± 6.0 (1–28)	RSP
	19 residences	NS	315–1,021	N/—	G/168 h	26.0 ± 22.6 (6–88)	RSP, repeat measures, source mix[e]
	11 residences	S	290–800	N/—	G/168 h	59.2 ± 38.8 (10–144)	RSP, repeat measures, source mix[e]

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TABLE 1. contd. (NRC, 1986)

Continued

Study	Type of Premise	Occupancy	Volume, m^3	Ventilation Type/Rate	Monitoring Type/Time	Concentrations Mean (range), $\mu g/m^3$	Comments
Parker et al., 1984	1 residence	NS T = 3	—	N/0.2-1.9 ach	0/24 h	<10 (—)	TSP
	2 residences	S = 1-2 T = 3-4	—	N/0.2-0.7 ach	0/24 h	10-46 (—)	TSP
Repace and Lowrey, 1980, 1982	Outdoors	—	—	—	P/2 min	42.9 (22-63)	RSP, average of 2-min samples
	27 Public buildings	0.13-3.54[f]	—	M/—	P/2 min	278 (86-1,140)	RSP, average of 2-min samples
Sexton et al., 1984	Outdoors 19 homes	—	—	—	G/24 h	17.0 ± 1.6 (6-23)	RSP, repeat samples
	24 residences	NS[c]	—	N/—	G/24 h	25.0 ± 1.0 (13-63)	Used fireplaces
Spengler et al., 1981	Outdoors	—	—	—	G/24 h	21.1 ± 11.9 (—)	RSP, repeat measures
	35 residences	NS	—	N/—	G/24 h	24.1 ± 11.6 (—)	RSP, repeat measures
	15 residences	S = 1	—	N/—	G/24 h	36.5 ± 14.5 (—)	RSP, repeat measures
	5 residences	S = 2	—	N/—	G/24 h	70.4 ± 42.9 (—)	RSP, repeat measures
Spengler et al., 1985	Outdoors	—	—	N/—	G/24 h	18 ± 2.1 (—)	RSP, repeat measures
	73 residences	NS[e]	—	—	G/24 h	28 ± 1.1 (—)	RSP, repeat measures
	28 residences	S	—	—	G/24 h	74 ± 6.6 (—)	RSP, repeat measures
Sterling and Sterling, 1983	1 office	S restr.	—	—	G(?)/—	25.5 (15-36)	TSP
	22 offices	S	—	—	G(?)/—	31.7 (—)	TSP
U.S. Department of Transportation, 1971	8 domestic planes	S T = 27-110	—	M/—	G/1-1/4, 2-1/2 h	Not given (—)	TSP
	20 military planes	S T = 165-219	—	M/—	G/6-7 h	<10-120 (—)	TSP
Webel and Fischer, 1980	44 offices	S	—	N,M/—	P/2 min (30 ea)	133 ± 130 (962 peak)	RSP, minus background level

[a] Active smokers per 100 m^3.
[b] Grams of tobacco consumed.
[c] Some smoking was reported during 9 of the 280 samples.
[d] Measured during 24-h periods by the perfluorocarbon tracer technique.
[e] Some residences had combinations of sources (kerosene heaters, wood stoves, etc.) and no cigarettes.
[f] Active smokers density per 100 m^3.

ABBREVIATIONS:
ach = Air changes per hour
G = Gravimetric
M = Mechanical ventilation
N = Natural ventilation
NS = No smokers
O = Optical monitor
P = Piezoelectric balance
QCMI = Quality Crystal Microbalance Cosade Impactor
RSP = Respirable suspended particles
S = Smokers
T = Total occupants
TSP = Total suspended particles
restr. = building with smoking restrictions

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Table 2. Number of persons 17 years and over, by cigarette smoking status, race, sex, and age: United States, 1980, (National Center for Health Comm.)

Race, Sex, and Age	Total Population	All Smoker	Present Smokers		Former Smokers		Never smoked	All occasional smoked
			Regular and/or Occasional	Regular smoker only	Regular and/or occasional	Regular smoker only		
All races			Numbers in Thousands					
Both Sexes 17 yrs.	160798	86611	52442	51770	33130	30731	74086	3486
17-24 years	32176	13286	10069	9827	3009	2632	18890	652
25-44 years	61042	35258	22916	22656	11985	11167	28754	1269
45-64 years	43556	27170	15336	15236	11474	10541	16330	1144
65 years & over	24024	10896	4121	4050	6664	6341	13112	421
Male ≥ 17 years	75970	49048	27751	27445	20672	19297	26906	1994
17-24 years	15699	6640	5018	4866	1504	1303	9039	405
25-44 years	23549	19696	12591	12503	6886	6393	9837	692
45-64 years	20830	16238	8402	8357	7612	7113	4593	645
65 year & over	9891	6473	1760	1718	4670	4488	3413	253
Female≥ 17 years	84828	37563	24690	24325	12452	11434	47180	1492
17-24 years	16477	6646	5051	4961	1504	1379	9832	248
25-44 years	22725	15562	10345	10152	5099	4774	15917	577
45-64 years	31472	10933	6933	6880	3862	3423	11737	499
65 years & over	14133	4423	2361	2333	1993	1853	9694	168
White≥ 17yrs.	139036	76041	45090	44515	30197	27976	62910	3045
17-24 years	27095	11525	8582	8400	2758	2463	15569	566
25-64 years	51889	30336	19723	19211	10728	9955	21471	1063
45-64 years	38470	24160	13383	13284	10480	9622	14269	1036
65 years & over	21635	10019	3676	3619	6231	5935	11600	380
Male	65941	43124	23654	23435	19025	17732	22802	1735
Female	73095	32917	21416	21079	11171	10244	40108	1310
Black≥ 17yrs.	16767	8314	5903	5831	2209	2045	8439	350
17-24 years	4094	1451	1264	1226	158	142	2643	* 56
25-44 years	6584	3656	2657	2624	874	829	2928	159
45-64 years	4071	2471	1636	1636	785	711	1586	*108
65 years & over	2018	736	346	346	391	369	1282	* 26
Male	7465	4512	3136	3078	1258	1192	2953	184
Female	9302	3802	2767	2753	950	853	5486	166

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TABLE 3. (Repace and Lowrey, 1985)

Time spent in various microenvironments by persons in 44 U.S. cities, expressed in average hours per day. (Ott, in press; NRC, 1981; Szalai, 1972).

Microenvironment	Employed Men, All Days	Employed Women, All Days	Married Housewives, All Days
Inside one's home	13.4	15.4	20.5
Just outside one's home	0.2	0.0	0.1
At one's workplace	6.7	5.2	–
In transit	1.6	1.3	1.0
In other people's homes	0.5	0.7	0.8
In places of business	0.7	0.9	1.2
In restaurants and bars	0.4	0.2	0.1
In all other locations	0.5	0.3	0.3
Total	24.0	24.0	24.0

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TABLE 4. COTININE IN NONSMOKERS FROM DOMESTIC AND NONDOMESTIC EXPOSURES.(NRC, 1986) 91% of the ETS exposure of the nonsmoking husbands of smoking wives came from non-domestic sources compared to 71% of the exposure of the nonsmoking husbands of smoking wives. The most probable non-domestic source of exposure is the workplace.

Urinary Cotinine Concentration and Number of Reported Hours of Exposure to Other People's Tobacco Smoke Within the Past 7 Days in Nonsmoking Married Men According to Smoking Habits of Their Wives

Smoking Category of Wife	No. of Men	Urinary Cotinine Concentration, ng/ml		Exposure to Other People's Smoke in Preceding Week, h			
				Total		Outside Home	
		Mean (SE)	Median	Mean (SE)	Median	Mean (SE)	Median
Nonsmoker	101	8.5(1.3)[a]	5.0	11.0(1.2)[b]	6.5	10.0(1.2)[c]	6.0
Smoker	20	25.2(14.8)	9.0	23.2(4.1)	21.1	16.4(3.3)	10.7

NOTE: Differences (nonsmoking wife versus smoking wife): [a] $p < 0.05$; [b] $p < 0.001$; [c] $p < 0.06$ (Wilcoxin rank sum test).

SOURCE: Wald and Ritchie (1984).

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TABLE 5. (SG, 1986).

—Cotinine measures in nonsmokers with environmental smoke exposure and comparisons with active smoking

Study	Number of subjects	Smoking status	Exposure level	Mean or median concentration and range: Plasma cotinine (ng/mL) Before	Plasma cotinine (ng/mL) After	Urine cotinine (ng/mL) Before	Urine cotinine (ng/mL) After	Saliva cotinine (ng/mL) Before	Saliva cotinine (ng/mL) After
Jarvis et al. (1983)	7	NS	Before, 11:30 a.m. After, public house x 2 hr	1.1	7.3	4.8	12.9	1.5	8.0
Jarvis et al. (1984)			Hospital clinic patients						
	46	NS	No exposure	—	0.8	—	1.5	—	0.7
	27	NS	Little exposure	—	1.8	—	4.5	—	2.2
	20	NS	Some exposure	—	2.5	—	5.6	—	2.8
	7	NS	Lot of exposure	—	1.8	—	9.4	—	2.6
	94	S		—	275	—	1391	—	310
Hoffmann et al. (1984)	10	NS	Experimental chamber						
			2 cigs burned	1.7	2.6 (peak	14	21	1.2	2.3
			3 cigs burned	1.0	3.0 change)	14	38	1.7	2.6
			4 cigs burned	0.9	3.3	14	86	1.0	1.4
Wald and Boreham (1984)	101	NS	Wife abstinent	—	—	8.6 (median 8.0)			
	20	NS	Wife smoker	—	—	26.2 (median 9.0)			

Study	Number of subjects	Smoking status	Exposure level	Mean or median concentration and range: Plasma cotinine (ng/mL) Before	Plasma cotinine (ng/mL) After	Urine cotinine (ng/mL) Before	Urine cotinine (ng/mL) After	Saliva cotinine (ng/mL) Before	Saliva cotinine (ng/mL) After
Wald et al. (1984)			Mail screening clinic patients						
	221	NS	Research colleagues			—	11.2		
	43	NS	0–1.5 hr ETS exposure/wk			—	2.8		
	47	NS	1.5–4.5 hr ETS exposure/wk			—	3.4		
	43	NS	4.5–8.6 hr ETS exposure/wk			—	5.3		
	43	NS	8.6–20 hr ETS exposure/wk			—	14.7		
	46	NS	20–80 hr ETS exposure/wk			—	28.6		
	131	S	Cigarettes			—	1646 (837–3328)		
	88	S	Cigars			—	386 (61–2138)		
	42	S	Pipes			—	1920 (1008–4589)		
Matsukura et al. (1984)	200	NS	No home exposure			—	810*		
	272	NS	All home exposure			—	780		
			Home exposure:						
	26	NS	1–9 cig/day			—	310		
	87	NS	10–19 cig/day			—	420		
	99	NS	20–29 cig/day			—	870		
	36	NS	30–39 cig/day			—	1030		
	28	NS	>40 cig/day			—	1560		
	472	NS	All			—	680		
	392	S	All			—	8620		
	76	NS	No workplace exposure			—	220		
	201	NS	Workplace exposure			—	720		

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TABLE 5.. cont'd. (SG, 1986).

Study	Number of subjects	Smoking status	Exposure level	Mean or median concentration and range: Plasma cotinine (ng/mL) Before	Plasma cotinine (ng/mL) After	Urine cotinine (ng/mL) Before	Urine cotinine (ng/mL) After	Saliva cotinine (ng/mL) Before	Saliva cotinine (ng/mL) After
Greenberg et al. (1984)	32	NS, infants	S mother			—	351 (41-1886)	—	9 (0-25)
	19		NS mother			—	4 (0-125)	—	0 (0-3)
Jarvis et al. (1985)	289	NS	Children aged 11-16 Neither parent SM					—	0.4 (median
	96	NS	SM father					—	1.3 (1.0)
	76	NS	SM mother					—	2.0 (1.7)
	128	NS	Both parents SM					—	3.4 (2.4)
Lusk and Nau (1986)	10	NS, neonates	No exposure	—	—	—	0' (0-66)	—	—
	19	NS, neonates	Nursed by S mother: no ETS exposure	—	—	—	100 (10-655)	—	—
	10	NS, infants	S mother, not nursed	—	—	—	227 (117-780)	—	—
	9	NS, infants	S mother, nursed; ETS exposure	—	—	—	560 (225-870)	—	—
				Serum cotinine (ng/mL)					
Pattenhall et al. (1986)e-	20	NS, children	Smokers in home	—	4.1	—	—	—	—
	18	NS, children	No smokers in home	—	1.0	—	—	—	—

Study	Number of subjects	Smoking status	Exposure level	Mean or median concentrations and range: Plasma cotinine (ng/mL) Before	Plasma cotinine (ng/mL) After	Urine cotinine (ng/mL) Before	Urine cotinine (ng/mL) After	Saliva cotinine (ng/mL) Before	Saliva cotinine (ng/mL) After
Coultas et al. (1989)	68	NS aged <6	No smokers in home	—	—	—	—	—	0, 1.7*
	41	NS aged <6	1 smoker in home	—	—	—	—	—	3.8, 4.1
	21	NS aged <6	2 or more smokers in home	—	—	—	—	—	5.4, 8.6
	200	NS aged 6-17	No smokers in home	—	—	—	—	—	0, 1.3
	98	NS aged 6-17	1 smoker in home	—	—	—	—	—	1.8, 2.6
	28	NS aged 6-17	2 or more smokers in home	—	—	—	—	—	5.3, 8.6
	316	NS aged >17	No smokers in home	—	—	—	—	—	0, 1.5
	60	NS aged >17	1 smoker in home	—	—	—	—	—	0.6, 2.8
	12	NS aged >17	2 or more smokers in home	—	—	—	—	—	0, 3.7

[illegible] morning specimens.
[illegible] means.

Source: https://www.industrydocuments.ucsf.edu/docs/gzvl0000

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TABLE 6. Estimated average nonsmokers' exposures to RSP from ETS at home and at work.(Repace and Lowrey, 1985) The concentrations are calculated for model home and workplace microenvironments and are weighted by average respiration rates and time budget-studies for percent of time spent at home and at work by male and female nonsmokers. The typical nonsmoker is estimated to be exposed to from 0 to 14 mg of RSP from ETS per day, with an average exposure of 1.5 mg/day.

Lifestyle: Daily Average Probability of Being Exposed (Rounded Values)		Exposure (mg) Modeled Daily Average	Daily Probability-Weighted
At work and at home: %	63 x 62 = 39	2.27	0.89
Neither at work nor at home: %	37 x 38 = 14	0.00	0.00
At home but not at work: %	62 x 37 = 23	0.45	0.10
At work but not at home: %	63 x 38 = 24	1.82	0.44
Total: %	100		1.43

The average nonexclusive probability of a nonsmoker being exposed to ETS at work is estimated as 63%; the probability of not being exposed at work is 37%; the nonexclusive probability of being exposed to ETS at home is estimated as 62%; the probability of not being exposed at home is 38%.

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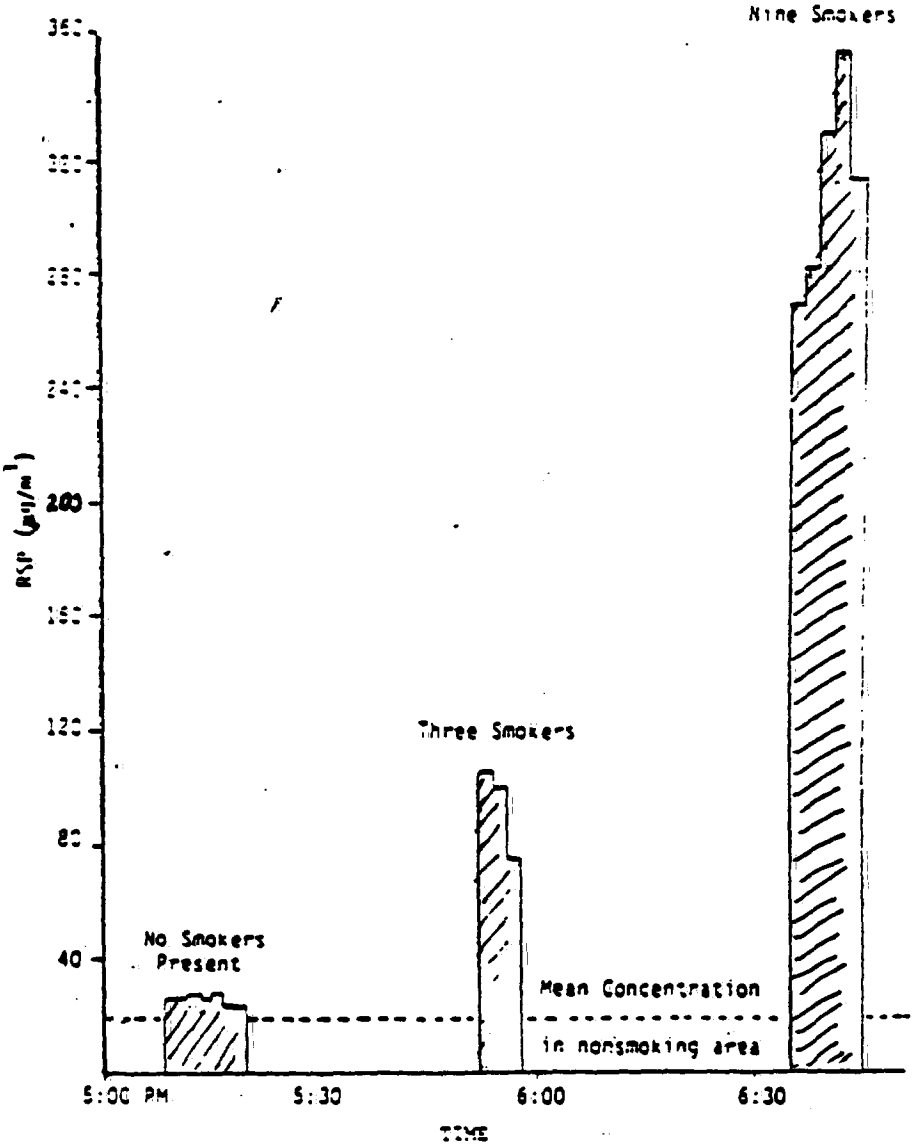
Source: https://www.industrydocuments.ucsf.edu/docs/gzvl0000

FIGURE 1 EPA's TEAM Study demonstrates that smoking provides the dominant source of RSP in many buildings (Sheldon, et al, 1986)



Respirable particulates in 3rd floor lounge of the elderly home-1 (1 24 83).

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Source: https://www.industrydocuments.ucsf.edu/docs/gzvl0000

FIGURE 2 Air exchange rates in homes are one determinant of nonsmokers' exposures to ETS. Low air exchange rates mean higher exposures. Shown is a histogram of infiltration values in a sample of 266 older US middle class homes around the country. Average heating season values are shown. The median of the distribution is 0.9 ach and the mean is 1.1 ± 0.9 ach.(Grot and Clark, 1979)(NRC, 1986)

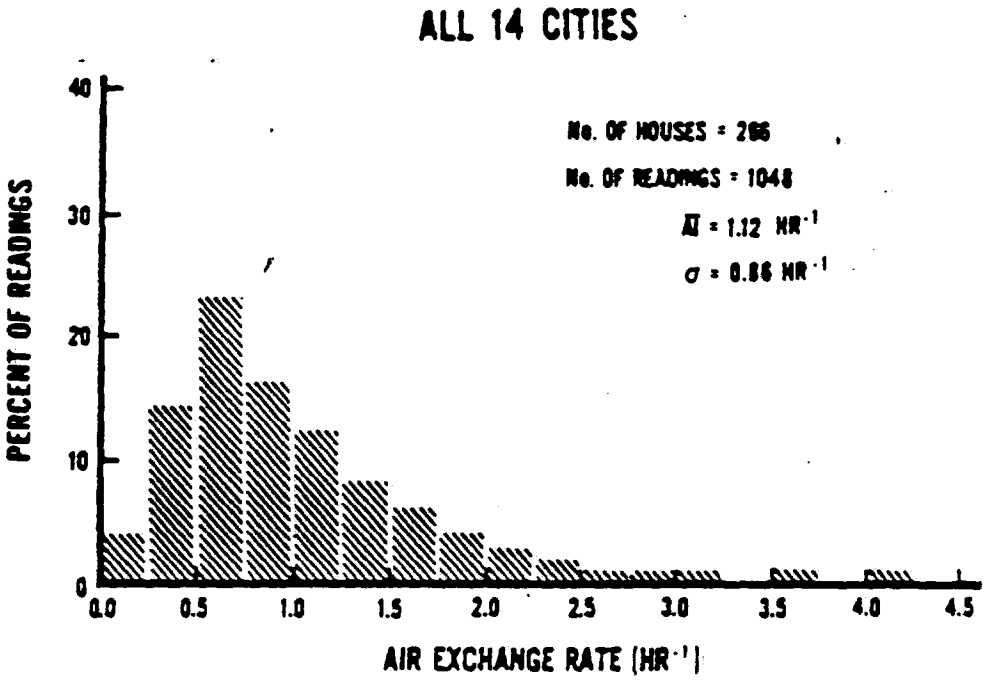

Figure 3. Histogram of measured natural air infiltration rates for 14 weatherization sites

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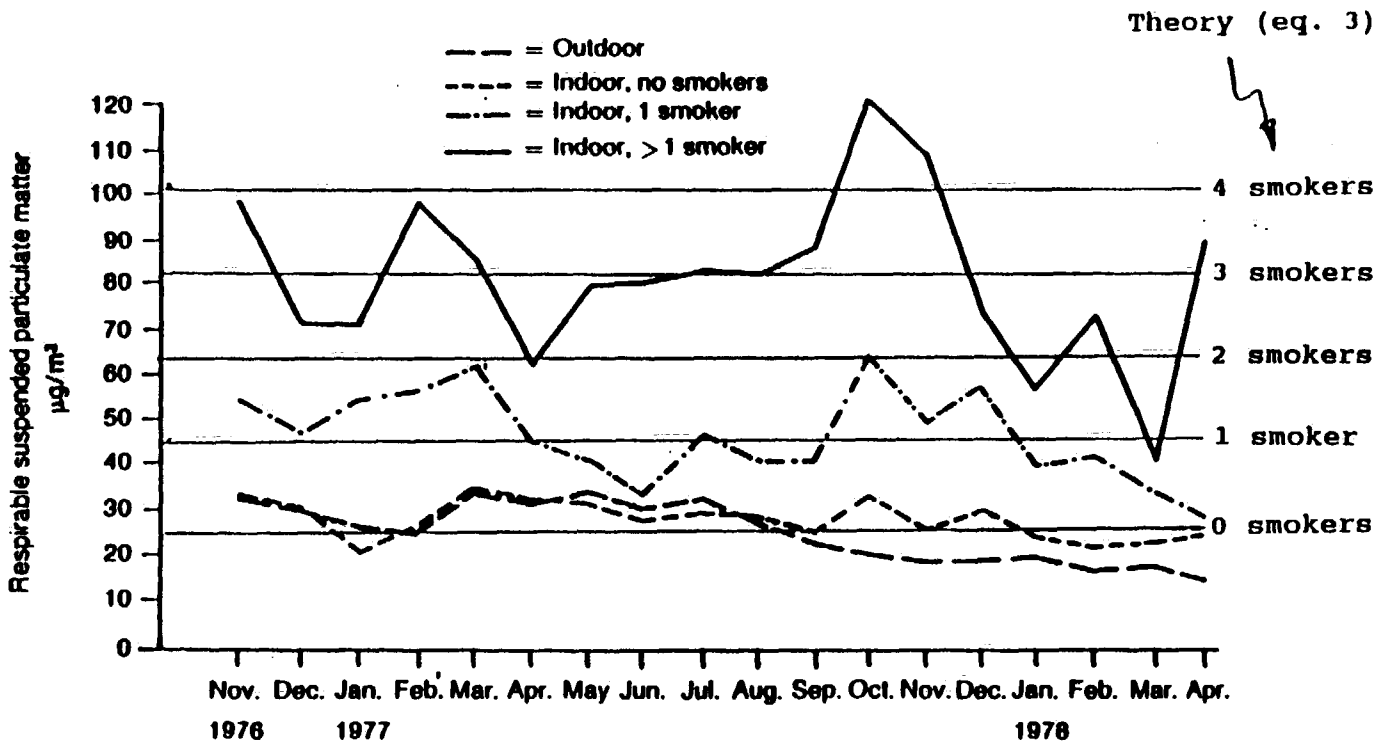

FIGURE 3. -- Comparison of predictions of RSP model for smoking in single-family homes with field data (Spengler et al., 1981) for monthly mean RSP concentrations for 55 homes in 6 Cities.

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FIGURE 4 The effect of smoking on workplace RSP levels in a Minneapolis office building. The contrast between daytime RSP levels, when smoking occured, and night-time RSP levels, when it did not, is marked.

Aerosol mass concentration in a 700-m^3 office with one smoker (Nelson *et al.* 1982). The smoking instrument and smoking rate were not specified. However, the air exchange rate for the space may be calculated by means of equation 2. For the decay of ETS on Thursday, July 9, a non-linear regression analysis of the RSP levels, with an 18 $\mu g/m^3$ background level subtraction, yields $C_a = 1.0$ ach ($r^2 = 0.95$). This value is close to the ASHRAE-recommended ventilation rate for office space.

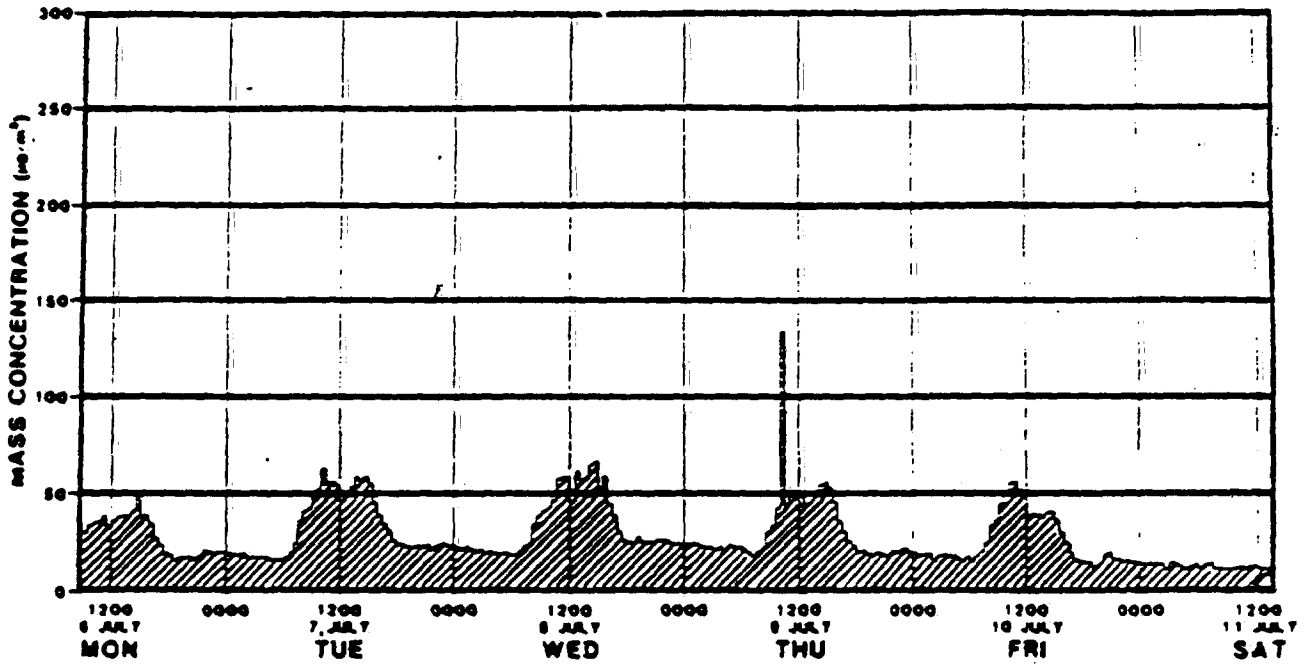

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FIGURE 5 Air exchange rates in commercial buildings are one determinant of nonsmokers' exposures to ETS in the workplace. Shown are air exchange rates (infiltration plus ventilation) in eight large federal office buildings in 8 US cities in 7 states. Air exchange rates in the tighter buildings failed to meet ASHRAE standards for occupied office space, (20 cfm/occ or 0.84 ach). The mean annual air exchange rate for all eight office buildings is 0.71 ± 0.25 air changes per hour, about one third less than in the sample of homes in fig. 2 . (Grot and Persily, 1986).

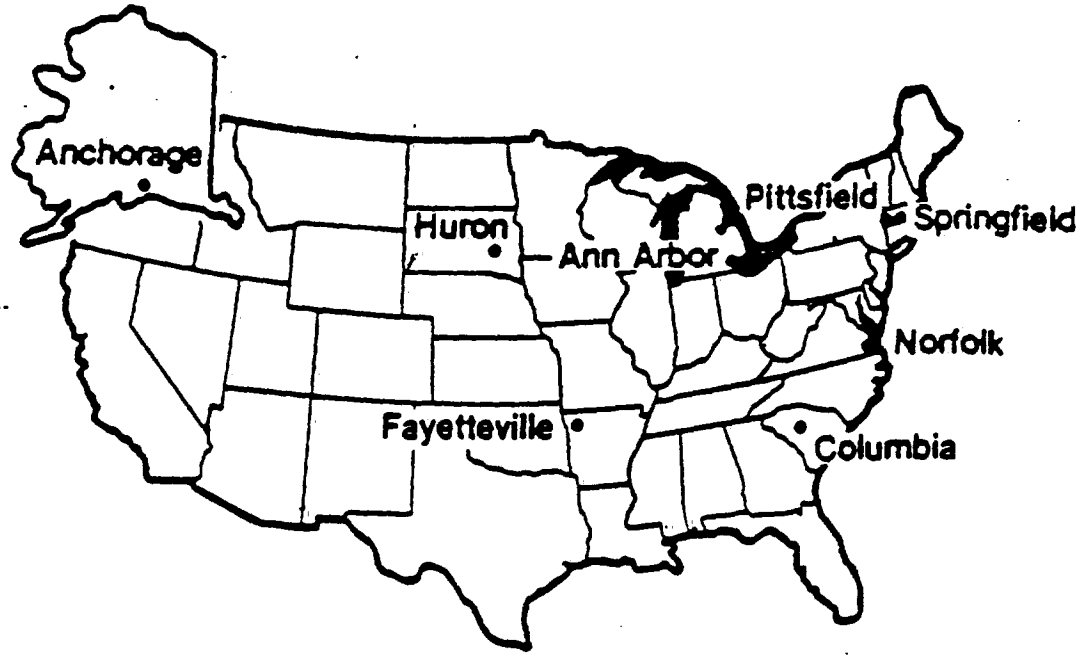

FIG. 1—*Location of the eight federal office buildings.*

BUILDING DIMENSIONS (100 m^2 ≅ 1000 ft^2)

Location	Occupiable Floor Area, m^2	Volume, m^3	Air exchange rate (ach)
Anchorage	45 500	174 000	0.82 ± .35
Ann Arbor	4 900	31 700	1.04 ± .69
Columbia	24 700	159 000	0.85 ± .23
Fayetteville	3 400	21 300	0.37 ± .09
Huron	6 420	27 500	0.32 ± .16
Norfolk	17 300	60 300	0.79 ± .19
Pittsfield	1 730	8 520	0.70 ± .19
Springfield	13 500	57 700	0.79 ± .18

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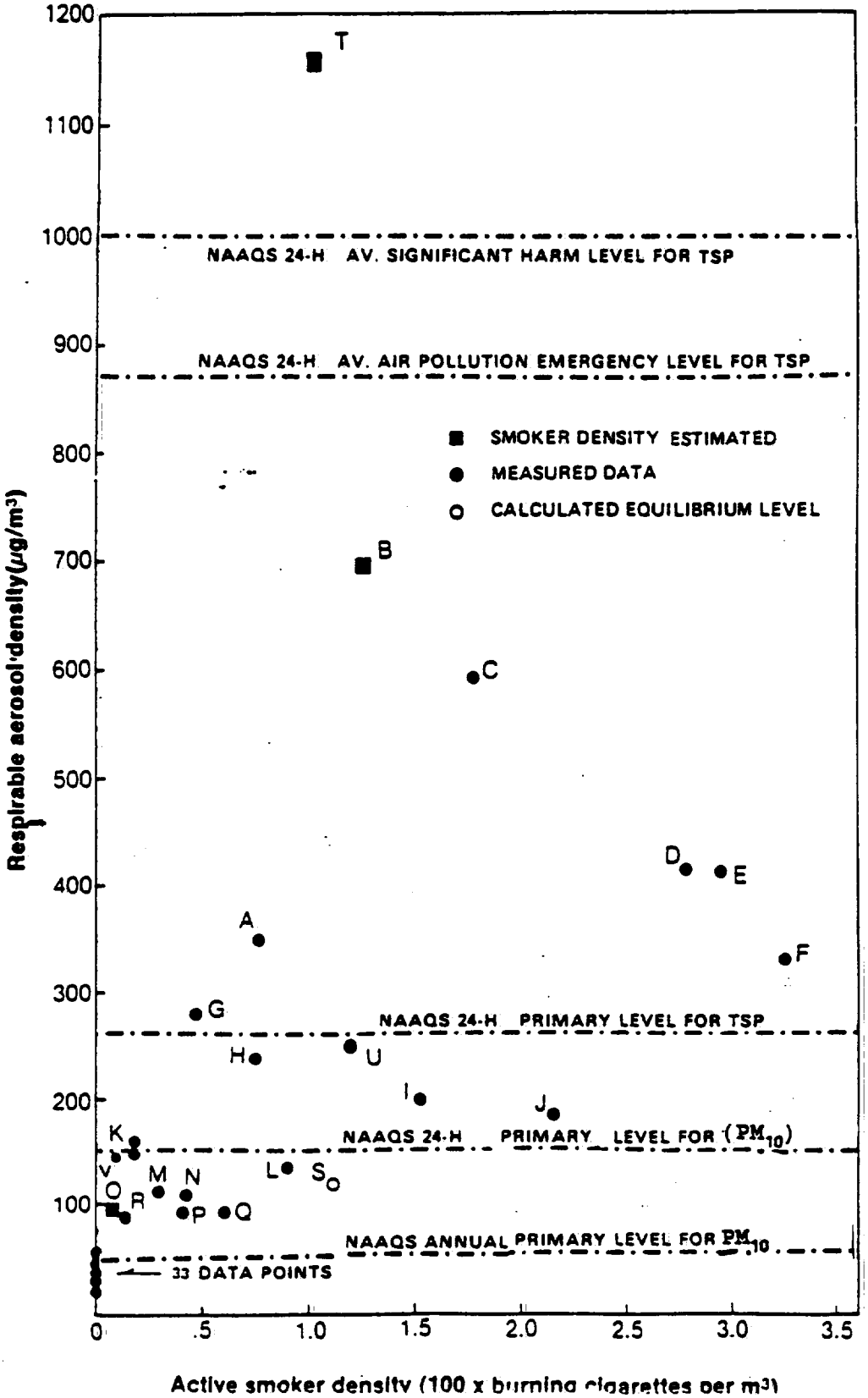
Source: https://www.industrydocuments.ucsf.edu/docs/gzvl0000

Figure 6. Indoor air pollution from ETS aerosol. Indoor levels of respirable particles in buildings where tobacco is smoked (data points (A-T)) greatly exceed those in which smoking is prohibited (unlabeled), and exceed the levels for health-based U.S. ambient air quality standards.



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